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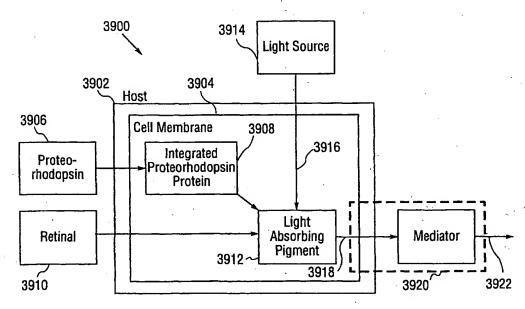
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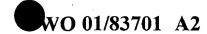
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(54) Title: LIGHT-DRIVEN ENERGY GENERATION USING PROTEORHODOPSIN



(57) Abstract: A light-driven energy generation system using proteorhodopsin is provided. Proteorhodopsin sequences were retrieved and amplified from naturally occurring members of the domain Bacteria using proteorhodopsin-specific polymerase chain reaction primers. Proteorhodopsin sequences were placed in expression vectors for production of proteorhodopsin proteins in a host, for instance, E. coli and other bacteria. The system also includes a light source and a source of retinal, that allows the system to convert light into biochemical energy. The generated biochemical energy could be mediated into electrical energy by a mediator.







For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

#### PATENT APPLICATION

# LIGHT-DRIVEN ENERGY GENERATION USING PROTEORHODOPSIN

#### **INVENTORS**

### Edward F. DeLong and Oded Beja

#### CROSS-REFERENCE TO RELATED APPLICATIONS

This application is cross-referenced to and claims priority from U.S Provisional application 60/201,602 filed 05/03/2000, which is hereby incorporated by reference.

### STATEMENT REGARDING FEDERALLY SPONDORED RESEARCH OR DEVELOPMENT

This invention was supported in part by grant number OCE 0001619 from the National Science Foundation (NSF). The U.S. government has certain rights in the invention.

## STATEMENT TO COMPUTER DISK AND SEQUENCE LISTING

This application includes a sequence listing of 65 sequences and a computer disk labeled "Sequence Listing for application entitled "Light-driven energy generation using proteorhodopsin" by Edward F. DeLong and Oded Beja" containing files "MBA101-SEQLIST.prj", dated "04/23/01" with 174,089 bytes, which is the PatentIn

project file generated using PatentIn Version 3.0 software provided by the USPTO, and "MBA101-SEQLIST.txt", dated "04/23/01" with 323,739 bytes, which is the generated sequence listing from the PatentIn project file MBA101-SEQLIST.prj using PatentIn Version 3.0 software, all which are herein incorporated. The information recorded in computer readable format on the incorporated computer disk labeled "Sequence Listing" containing files "MBA101-SEQLIST.prj" and "MBA101-SEQLIST.txt" are identical to the incorporated written sequence listing.

#### FIELD OF THE INVENTION

The present invention relates generally to gene expression of functional recombinant proteins in bacteria. More particularly, the present invention relates to proteorhodopsin genes and proteins that function as a light-driven energy generator in *Escherichia coli* (E. coli) and other bacteria.

#### **BACKGROUND ART**

Retinal (vitamin A aldehyde) is a chromophore that binds integral membrane proteins (opsins) to form light-absorbing pigments called rhodopsins. Rhodopsins are currently known to belong to two distinct protein families. The visual rhodopsins, found in the eye throughout the animal kingdom, are photosensory pigments. Archeal rhodopsins, found in extreme halophilic environments, function as light-driven protons pumps (bacteriorhodopsins), chloride ion pumps (halorhodopsins), or photosensory receptors (sensory rhodopsins). The two protein families show no significant sequence similarity and may have different origins. They do, however, share identical topologies characterized by seven transmembrane  $\alpha$ -helices that form a pocket in which retinal is covalently linked, as a pronated Schiff base (helix G).

The archaeal rhodopsins are able to generate a photocycle which produces a chemiosmotic membrane potential in response to light, as such light energy is converted into biochemical energy. Recently, a protein with high sequence similarity to the archaeal rhodopsins has also been retrieved in the eukaryote Neurospora crassa (J.A. Bieszke et al., Proceedings of National Academy of Sciences USA 96:8034, 1999). The eucaryal rhodopsin formed a photochemically reactive pigment when bound to all-trans retinal and exhibited photocycle kinetics similar to those of archaeal sensory rhodopsins (J.A. Bieszke et al., Biochemistry 38:14138, 1999). To date, however, no rhodopsin-like sequences have been reported in members of the domain Bacteria, and no light-driven proton pumps based on rhodopsin have ever before been functionally expressed in E coli.

The phototropic conversion of light energy into biochemical energy using bacteriorhodopsin can be harnessed for a variety of processes and applications, such as bio-electronic applications and bio-materials, as has been reported in US Patent No. 5,757,525 for optical devices, US Patent No. 5,854,710 for optical Fourier processing, and US Patent No. 5,470,690 for optical information storage. Bacteriorhodopsin in bio-electronic applications is aimed to interface, integrate, or substitute the silicon based microelectronics systems as well as molecular devices. Bacteriorhodopsin as a bio-material is integrated, for instance, in optical films for light mediated computer memory applications and pattern recognition.

Prevsiously, archaeal rhodopsins capable of generating a chemiosmotic membrane potential in response to light had only been found in halophilic archaea. Therefore, rhodopsins that originate from archaea adapted to highly saline environments cannot be functionally expressed in *E. coli*. Finally, the isolation and cultivation of

halorhodopsins is an elaborate process. At present one does not foresee an economic utilization possible for this process (e.g. US Patent 5,290,699).

Accordingly, as one skilled in the art might readily acknowledge, there is a strong need to retrieve and provide rhodopsin-like sequences from naturally occurring members of the domain Bacteria.

#### **OBJECTS AND ADVANTAGES**

In light of the above, it is the primary objective of the present invention to provide rhodopsin-like sequences from naturally occurring members of the domain Bacteria. More specifically, it is the objective of the present invention to provide a method to retrieve proteorhodopsin genes from DNA of naturally occurring bacteria that encodes DNA sequence for proteorhodopsin proteins.

It is another objective of the present invention to provide proteorhodopsin-specific polymerase chain reaction primers that amplify the proteorhodopsin-containing gene from a DNA sample of naturally occurring bacteria.

It is yet another objective of the present invention to produce variants of a proteorhodopsin gene using the same proteorhodopsin-specific polymerase chain reaction primers by amplifying a proteorhodopsin-containing gene from of a mixed sample of naturally occurring bacteria.

It is still another objective of the present invention to provide an expression vector that produces a proteorhodopsin protein in *E. coli* and other bacteria.

It is another objective of the present invention to provide a light-driven energy generator in which the functional properties of proteorhodopsin are utilized. These properties include the ability to integrate within a host, for instance a cell membrane of *E. coli*, making an integrated proteorhodopsin protein, and the ability to bind retinal, making a light absorbing pigment.

It is another objective of the present invention to provide a light source and illuminate the light absorbing pigment to convert light energy into biochemical energy.

It is another objective of the present invention to provide a mediator and mediate the biochemical energy into electrical energy.

It is another objective of the present invention to provide methods to manipulate the kinetics of the light-driven energy generator.

The advantage of the present invention over the prior art is that it is not restricted to operate in halophilic archaea and could therefore be functionally expressed in *E. coli* and other bacteria. Accordingly, another advantage of the present invention is that it provides for a fast and cheap production method that allows for mass production of functionally active proteorhodopsin.

#### SUMMARY

The present invention provides proteorhodopsin gene and protein sequences retrieved from samples of naturally occurring members of the domain Bacteria. More specifically, the present invention provides a method for the retrieval and amplification of proteorhodopsin genes from DNA samples of naturally occurring marine bacteria. In accordance with several exemplary embodiments of the present invention, DNA samples were obtained from naturally occurring bacteria such as, for instance, marine proteobacteria, SAR86 bacteria, or recombinant DNA libraries containing naturally occurring bacteria. The present invention provides proteorhodopsin-specific polymerase chain reaction (PCR) primers to amplify a proteorhodopsin gene from DNA samples of these marine bacteria. The present invention also provides a device and method for the placement of proteorhodopsin genes in an expression vector to produce functional proteorhodopsin proteins in *E. coli* and other bacteria.

Accordingly, the present invention provides a method to produce and obtain variants of proteorhodopsin genes and proteins. The same proteorhodopsin-specific polymerase chain reaction primers amplify different variants of proteorhodopsin-containing genes from a mixed sample of naturally occurring bacteria. As one skilled in the art might readily acknowledge, these variants of a proteorhodopsin gene produce functional variations in the photocycle kinetics of the proteorhodopsin protein.

Furthermore, the present invention provides a light-driven energy generator that utilizes proteorhodopsin to convert light-energy into biochemical energy. This light-driven energy generator takes advantage of the functional properties of the proteorhodopsin protein once expressed in, for example, *E. coli* or other bacteria as is

described in exemplary embodiments. These properties include the ability to integrate within a host such as, for instance, a cell membrane of *E. coli* or other Bacteria, and thereby making an integrated proteorhodopsin protein or integrated cell membrane protein. These properties also include the ability to bind retinal and thereby making a light absorbing pigment. Illuminating the light absorbing pigment with a light source converts light energy into biochemical energy. Finally, the biochemical energy can be mediated into electrical energy by a mediator.

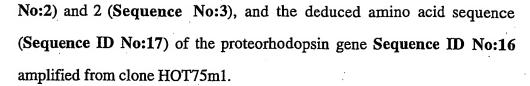
In accordance with exemplary embodiments, the present invention enables one skilled in the art to manipulate the kinetics of the proteorhodopsin protein photocycle once it is operational in the light-driven energy generator. In particular, the present invention provides examples in which the light source characteristics are manipulated. Examples are the manipulation of the delivery of fast-light pulses and/or the delivery of light at different wavelengths. The present invention also provides examples in which incremental additions of retinal influences the function of the light-driven energy generator. In addition, a proteorhodopsin gene or protein variant can be selected to determine an absorption spectra of the light absorbing pigment to change the kinetics of the light energy generator, for instance to meet a design/functional criteria of an application wherein proteorhodopsin is utilized.

# BRIEF DESCRIPTION OF THE FIGURES

The objectives and advantages of the present invention will be understood by reading the following detailed description in conjunction with the drawings, in which:

- FIG. 1 illustrates the phylogenetic tree of bacterial 16S rRNA gene sequences including that encoded on the 130 kb bacterioplankton BAC clone (EBAC31A8).
- FIG. 2 provides a nucleotide sequence of polymerase chain reaction primer 1 (Sequence ID No:2) used to amplify a proteorhodopsin gene.
- FIG. 3 provides a nucleotide sequence of polymerase chain reaction primer 2 (Sequence ID No:3) used to amplify a proteorhodopsin gene.
- FIG. 4 provides the nucleotide sequence of the proteorhodopsin gene (Sequence ID No:4) amplified from clone EBAC31A8 (Sequence ID No:1) using PCR primers 1 (Sequence ID No:2) and 2 (Sequence ID No:3), and the deduced amino acid sequence (Sequence ID No:5) of the proteorhodopsin gene Sequence ID No:4 amplified from clone EBAC31A8 (Sequence ID No:1).
- FIG. 5 provides a map of the secondary structure of the proteorhodopsin protein (Sequence ID No:7). Single letter amino acid codes are used (according to J. Sasaki and J.L. Spudich, Biophys. J. 75:2435, 1998). Predicted retinal binding pocket residues are marked in black.
- FIG. 6 provides the nucleotide sequence of the proteorhodopsin gene (Sequence ID No:8) amplified from clone EBAC40E8 using PCR primers 1 (Sequence ID No:2) and 2 (Sequence No:3), and the deduced amino acid sequence (Sequence ID No:9) of the proteorhodopsin gene Sequence ID No:8 amplified from clone EBAC40E8.
- FIG. 7 provides the nucleotide sequence of the proteorhodopsin gene (Sequence ID No:10) amplified from clone EBAC41B4 using PCR primers 1 (Sequence ID No:2) and 2 (Sequence No:3), and the deduced amino acid sequence (Sequence ID No:11) of the proteorhodopsin gene Sequence ID No:7 amplified from clone EBAC41B4.

- FIG. 8 provides the nucleotide sequence of the proteorhodopsin gene (Sequence ID No:12) amplified from clone EBAC64A5 using PCR primers 1 (Sequence ID No:2) and 2 (Sequence No:3), and the deduced amino acid sequence (Sequence ID No:13) of the proteorhodopsin gene Sequence ID No:12 amplified from clone EBAC64A5.
- FIG. 9 provides a variants map of the DNA sequences of the proteorhodopsin gene with Sequence ID No:4, Sequence ID No:8, Sequence ID No:10, and Sequence ID No:12 that were amplified from clone EBAC38A8, EBAC40E8, EBAC41B4 and EBAC64A5 respectively using the proteorhodopsin-specific PCR primer 1 (Sequence ID No:2) and 2 (Sequence ID No:3). Dots represent sequences having identical sequence as those in Sequence ID No:4.
- FIG. 10 provides a variant map of the deduced amino acid sequences encoded by the proteorhodopsin gene with Sequence ID No:4, Sequence ID No:8, Sequence ID No:10, and Sequence ID No:12 that were amplified from respectively EBAC38A8, EBAC40E8, EBAC41B4 and EBAC64A5 using the proteorhodopsin-specific primer 1 (Sequence ID No:2) and 2 (Sequence ID No:3). Lower case represents the PCR primer sequence region. Dots represent residues having identical sequence as those in Sequence ID No:5.
- FIG. 11 provides the nucleotide sequence of the proteorhodopsin gene (Sequence ID No:14) amplified from clone HOT0m1 using PCR primers 1 (Sequence ID No:2) and 2 (Sequence No:3), and the deduced amino acid sequence (Sequence ID No:15) of the proteorhodopsin gene Sequence ID No:14 amplified from clone HOT0m1.
- FIG. 12 provides the nucleotide sequence of the proteorhodopsin gene (Sequence ID No:16) amplified from clone HOT75m1 using PCR primers 1 (Sequence ID



- FIG. 13 provides the nucleotide sequence of the proteorhodopsin gene (Sequence ID No:18) amplified from clone HOT75m3 using PCR primers 1 (Sequence ID No:2) and 2 (Sequence No:3), and the deduced amino acid sequence (Sequence ID No:19) of the proteorhodopsin gene Sequence ID No:18 amplified from clone HOT75m3.
- FIG. 14 provides the nucleotide sequence of the proteorhodopsin gene (Sequence ID No:20) amplified from clone HOT75m4 using PCR primers 1 (Sequence ID No:2) and 2 (Sequence No:3), and the deduced amino acid sequence (Sequence ID No:21) of the proteorhodopsin gene Sequence ID No:20 amplified from clone HOT75m4.
- FIG. 15 provides the nucleotide sequence of the proteorhodopsin gene (Sequence ID No:22) amplified from clone HOT75m8 using PCR primers 1 (Sequence ID No:2) and 2 (Sequence No:3), and the deduced amino acid sequence (Sequence ID No:23) of the proteorhodopsin gene Sequence ID No:22 amplified from clone HOT75m8.
- FIG. 16 provides the nucleotide sequence of the proteorhodopsin gene (Sequence ID No:24) amplified from clone MB0m1 using PCR primers 1 (Sequence ID No:2) and 2 (Sequence No:3), and the deduced amino acid sequence (Sequence ID No:25) of the proteorhodopsin gene Sequence ID No:24 amplified from clone MB0m1.
- FIG. 17 provides the nucleotide sequence of the proteorhodopsin gene (Sequence ID No:26) amplified from clone MB0m2 using PCR primers 1 (Sequence ID No:2) and 2 (Sequence No:3), and the deduced amino acid sequence

- (Sequence ID No:27) of the proteorhodopsin gene Sequence ID No:26 amplified from clone MB0m2.
- FIG. 18 provides the nucleotide sequence of the proteorhodopsin gene (Sequence ID No:28) amplified from clone MB20m2 using PCR primers 1 (Sequence ID No:2) and 2 (Sequence No:3), and the deduced amino acid sequence (Sequence ID No:29) of the proteorhodopsin gene Sequence ID No:28 amplified from clone MB20m2.
- FIG. 19 provides the nucleotide sequence of the proteorhodopsin gene (Sequence ID No:30) amplified from clone MB20m5 using PCR primers 1 (Sequence ID No:2) and 2 (Sequence No:3), and the deduced amino acid sequence (Sequence ID No:31) of the proteorhodopsin gene Sequence ID No:30 amplified from clone MB20m5.
  - FIG. 20 provides the nucleotide sequence of the proteorhodopsin gene (Sequence ID No:32) amplified from clone MB20m12 using PCR primers 1 (Sequence ID No:2) and 2 (Sequence No:3), and the deduced amino acid sequence (Sequence ID No:33) of the proteorhodopsin gene Sequence ID No:32 amplified from clone MB20m12.
  - FIG. 21 provides the nucleotide sequence of the proteorhodopsin gene (Sequence ID No:34) amplified from clone MB40m1 using PCR primers 1 (Sequence ID No:2) and 2 (Sequence No:3), and the deduced amino acid sequence (Sequence ID No:35) of the proteorhodopsin gene Sequence ID No:34 amplified from clone MB40m1.
  - FIG. 22 provides the nucleotide sequence of the proteorhodopsin gene (Sequence ID No:36) amplified from clone MB40m5 using PCR primers 1 (Sequence ID No:2) and 2 (Sequence No:3), and the deduced amino acid sequence

- (Sequence ID No:37) of the proteorhodopsin gene Sequence ID No:36 amplified from clone MB40m5.
- FIG. 23 provides the nucleotide sequence of the proteorhodopsin gene (Sequence ID No:38) amplified from clone MB40m12 using PCR primers 1 (Sequence ID No:2) and 2 (Sequence No:3), and the deduced amino acid sequence (Sequence ID No:39) of the proteorhodopsin gene Sequence ID No:38 amplified from clone MB40m12.
- FIG. 24 provides the nucleotide sequence of the proteorhodopsin gene (Sequence ID No:40) amplified from clone MB100m5 using PCR primers 1 (Sequence ID No:2) and 2 (Sequence No:3), and the deduced amino acid sequence (Sequence ID No:41) of the proteorhodopsin gene Sequence ID No:40 amplified from clone MB100m5.
- FIG. 25 provides the nucleotide sequence of the proteorhodopsin gene (Sequence ID No:42) amplified from clone MB100m7 using PCR primers 1 (Sequence ID No:2) and 2 (Sequence No:3), and the deduced amino acid sequence (Sequence ID No:43) of the proteorhodopsin gene Sequence ID No:42 amplified from clone MB100m7.
- FIG. 26 provides the nucleotide sequence of the proteorhodopsin gene (Sequence ID No:44) amplified from clone MB100m9 using PCR primers 1 (Sequence ID No:2) and 2 (Sequence No:3), and the deduced amino acid sequence (Sequence ID No:45) of the proteorhodopsin gene Sequence ID No:44 amplified from clone MB100m9.
- FIG. 27 provides the nucleotide sequence of the proteorhodopsin gene (Sequence ID No:46) amplified from clone MB100m10 using PCR primers 1 (Sequence ID No:2) and 2 (Sequence No:3), and the deduced amino acid sequence

- (Sequence ID No:47) of the proteorhodopsin gene Sequence ID No:46 amplified from clone MB100m10.
- FIG. 28 provides the nucleotide sequence of the proteorhodopsin gene (Sequence ID No:48) amplified from clone PALB1 using PCR primers 1 (Sequence ID No:2) and 2 (Sequence No:3), and the deduced amino acid sequence (Sequence ID No:49) of the proteorhodopsin gene Sequence ID No:48 amplified from clone PALB1.
- FIG. 29 provides the nucleotide sequence of the proteorhodopsin gene (Sequence ID No:50) amplified from clone PALB2 using PCR primers 1 (Sequence ID No:2) and 2 (Sequence No:3), and the deduced amino acid sequence (Sequence ID No:51) of the proteorhodopsin gene Sequence ID No:50 amplified from clone PALB2.
- FIG. 30 provides the nucleotide sequence of the proteorhodopsin gene (Sequence ID No:52) amplified from clone PALB5 using PCR primers 1 (Sequence ID No:2) and 2 (Sequence No:3), and the deduced amino acid sequence (Sequence ID No:53) of the proteorhodopsin gene Sequence ID No:52 amplified from clone PALB5.
- FIG. 31 provides the nucleotide sequence of the proteorhodopsin gene (Sequence ID No:54) amplified from clone PALB7 using PCR primers 1 (Sequence ID No:2) and 2 (Sequence No:3), and the deduced amino acid sequence (Sequence ID No:55) of the proteorhodopsin gene Sequence ID No:54 amplified from clone PALB7.
- FIG. 32 provides the nucleotide sequence of the proteorhodopsin gene (Sequence ID No:56) amplified from clone PALB6 using PCR primers 1 (Sequence ID No:2) and 2 (Sequence No:3), and the deduced amino acid sequence

- (Sequence ID No:57) of the proteorhodopsin gene Sequence ID No:56 amplified from clone PALB6.
- FIG. 33 provides the nucleotide sequence of the proteorhodopsin gene (Sequence ID No:58) amplified from clone PALB8 using PCR primers 1 (Sequence ID No:2) and 2 (Sequence No:3), and the deduced amino acid sequence (Sequence ID No:59) of the proteorhodopsin gene Sequence ID No:58 amplified from clone PALB8.
- FIG. 34 provides the nucleotide sequence of the proteorhodopsin gene (Sequence ID No:60) amplified from clone PALE1 using PCR primers 1 (Sequence ID No:2) and 2 (Sequence No:3), and the deduced amino acid sequence (Sequence ID No:61) of the proteorhodopsin gene Sequence ID No:60 amplified from clone PALE1.
- FIG. 35 provides the nucleotide sequence of the proteorhodopsin gene (Sequence ID No:62) amplified from clone PALE6 using PCR primers 1 (Sequence ID No:2) and 2 (Sequence No:3), and the deduced amino acid sequence (Sequence ID No:63) of the proteorhodopsin gene Sequence ID No:62 amplified from clone PALE6.
- FIG. 36 provides the nucleotide sequence of the proteorhodopsin gene (Sequence ID No:64) amplified from clone PALE7 using PCR primers 1 (Sequence ID No:2) and 2 (Sequence No:3), and the deduced amino acid sequence (Sequence ID No:65) of the proteorhodopsin gene Sequence ID No:64 amplified from PALE7.
- FIG. 37 illustrates a phylogenetic tree of different proteorhodopsin genes.
- FIG. 38 provides an example of an alignment of proteorhodopsin amino acid sequences.
- FIG. 39 provides a light-driven energy generator that utilizes proteorhodopsin.

- FIG. 40 provides an example of a proteorhodopsin-expressing *E. coli* cell suspension (+) compared to control cells (-), both with all-trans retinal.
- FIG. 41 provides an example of absorption spectra of retinal-constituted proteorhodopsin in E coli membranes and a negative control.
- FIG. 42 provides an example of a light-driven transport of protons by a proteorhodopsin-expressing E. coli cell suspension.
- FIG. 43 provides an example of a transport of [<sup>3</sup>H]TPP<sup>+</sup> in E. coli right-side-out vesicles containing expressed proteorhodopsin, reconstituted with or without 10 μM retinal in the presence of light or in the dark.
- FIG. 44 provides an example of laser flash-induced absorbance changes in suspensions of *E. coli* membranes containing proteorhodopsin.
- FIG. 45 provides an example of absorption spectra of retinal-constituted proteorhodopsin in *E. coli* membranes.

#### DETAILED DESCRIPTION

Although the following detailed description contains many specifics for the purposes of illustration, anyone of ordinary skill in the art will appreciate that many variations and alterations to the following details are within the scope of the invention. Accordingly, the following preferred embodiment of the invention is set forth without any loss of generality to, and without imposing limitations upon, the claimed invention.

## Proteorhodopsin

The present invention provides rhodopsin-like gene and protein sequences retrieved from naturally occurring members of the domain Bacteria. More specifically, the present invention provides a method for the retrieval and amplification of proteorhodopsin genes from DNA samples of naturally occurring marine bacteria. In accordance with exemplary embodiments of the present invention, DNA samples were obtained from naturally occurring marine bacteria such as bacteria from the SAR86 group. Provided as an exemplary embodiment of the SAR86 group, DNA samples were obtained from a bacterioplankton Bacterial Artificial Chromosome (BAC) clone BAC31A8 (also referred to as EBAC31A08). In general, as will be appreciated by those of ordinary skill in the art, suitable DNA samples can also be obtained from other sources, e.g., from a marine environment or from a recombinant DNA library containing genomic fragments of samples of naturally occurring bacteria.

FIG. 1 shows the phylogenetic tree of bacterial 16S rRNA gene sequences including that encoded on the EBAC31A8. FIG. 1 also shows the relationship of EBAC31A8 to the SAR86 bacteria group as well as to the gamma-proteobacteria group. A subclone shotgun library was constructed from BAC clone 31A8, and subclones were sequenced in both directions on the MegaBACE 1000 capillary array electrophoresis DNA sequencing instrument (Molecular Dynamics, Sunnyvale, CA). Sequence analysis of a 130-kb genomic DNA that encodes the ribosomal RNA operon from BAC31A8, reveals an open reading frame encoding a proteorhodopsin. In an exemplary embodiment, the contiguous sequence was assembled using SEQUENCHER 3.1.1 software (Gene Codes Co., Ann Arbor, MI). Other sequencing techniques can also be used, as will be recognized by those skilled in the art. The sequence of the proteorhodopsin-containing contig has been deposited in GenBank under accession #AF279106 and deposit date October 23<sup>rd</sup>, 2000. Appendix A, hereby incorporated, shows the nucleotide sequence of the BAC clone BAC31A8 (Sequence ID No:1)

which contains the 130 kilobases genomic DNA from a naturally occurring marine bacterium.

Proteorhodopsin was amplified from the 130 kilobase bacterioplankton BAC clone 31A8 (Sequence ID No:1) by polymerase chain reaction (PCR), using the proteorhodopsin-specific primers 5'-aCCATGGgtaaattattactgatattagg-3' (Sequence ID No:2 and shown in FIG. 2) and 5'-agcattagaagattctttaacagc-3' (Sequence ID No:3 and shown in FIG. 3). References for PCR are, for instance, The Polymerase Chain Reaction, Mullis et al., Ed. (Birkhauser, Boston, 1994) and U.S. Patent Nos. 4,683,195 and 4,683,202 to Mullis et al. The proteorhodopsin-specific PCR primers include the addition of 3 nucleotides that encoded one amino acid not found in the native gene sequence of clone BAC31A8 (Sequence ID No:6), in the second amino acid position which is a glycine located on the 2<sup>nd</sup> codon ("GGT"). Therefore, compare the second amino acid position in the Sequence ID No:5 using PCR primers 1 and 2 with the native Sequence ID no:7. This addition of one non-native amino acid created a new restriction endonuclease site (NcoI site) not present in the native sequence. allowed subcloning of the amplified fragment into the NcoI restriction site of an expression vector pBAD TOPO TA Cloning® Kit (Invitrogen, La Jolla, CA). The present invention is not limited to the use of this type of expression vector and other expression vectors could also be used.

FIG. 4 shows the nucleotide sequence of the proteorhodopsin gene (Sequence ID No:4) that results from amplification of the proteorhodopsin-containing DNA in BAC31A8 using proteorhodopsin-specific PCR primers Sequence ID No:2 and Sequence No:3. FIG. 4 also shows the deduced amino acid sequences (Sequence ID No:5) encoded by the proteorhodopsin gene (Sequence ID No:4).

FIG. 5 shows an exemplary embodiment of a secondary structure of proteorhodopsin after it has been folded in a cell membrane 510 and bonded with retinal 520. FIG. 5 shows the native proteorhodopsin gene (Sequence ID No:6) obtained from clone BAC31A8 and encodes a proteorhodopsin protein of 249 amino acids with a molecular weight of 27 kD (Sequence ID No:7). In FIG. 5, 530 indicates seven transmembrane domains, a typical feature of the rhodopsin protein family, that aligned well with the corresponding helices of the archaeal rhodopsins. FIG. 5 also shows the amino acid residues that form a retinal binding pocket indicated by 520. Although the proteorhodopsin proteins shown in FIGS. 4 and 5 both originate from BAC31A8, they differ with respect to the second amino acid position. The reason is that the proteorhodopsin-specific PCR primers that were used to amplify the proteorhodopsin gene from BAC31A8 (which resulted in proteorhodopsin protein as in FIG. 4; Sequence ID No:5) included the addition of 3 nucleotides. These 3 nucleotides encoded one amino acid not found in the native gene sequence (Sequence ID No:6), in the second amino acid position which is a glycine located on the 2<sup>nd</sup> codon ("GGT"). Proteorhodopsin protein (Sequence ID No:7) as shown in FIG. 5 originates from the native gene sequence without the addition of the 3 nucleotides. As mentioned above, the addition of the 3 nucleotides created a new restriction endonuclease site (NcoI site) that was not present in the native sequence and thereby allowed the amplified fragment to be subcloned into the NcoI site of the expression vector.

In the exemplary embodiment presented above, PCR primers with Sequence ID No:2 and Sequence ID No:3 were used. In general, the present invention provides a method for designing different proteorhodopsin-specific PCR primers that are all capable of amplifying a proteorhodopsin gene from DNA samples of naturally occurring microbial populations by polymerase chain reaction. In designing these

primers one first needs to determine a DNA sequence of a proteorhodopsin gene. Then one can design oligodeoxynucleotide primers with a Watson-Crick base pair complementary to 5' and 3' ends of the proteorhodopsin gene.

#### Variants of Proteorhodopsin

In the previous section, an exemplary embodiment is provided of a proteorhodopsin gene and protein. The present invention also provides the retrieval of genetic variations of proteorhodopsin from naturally occurring genetic variations in naturally occurring bacterial populations. These genetic variations in proteorhodopsin sequences result in functional variations in the proteorhodopsin proteins as is discussed below.

The present invention enables one skilled in the art to use the same proteorhodopsin-specific PCR primers as shown in FIGS. 2 and 3 to successfully amplify different sequence variants from DNA originating from mixed naturally occurring bacterial populations when it is compared to for instance the proteorhodopsin gene as shown in FIG. 4. As mentioned above, different proteorhodopsin-specific PCR primers could be used to amplify genetic variants of proteorhodopsin.

FIGS. 6-8 show exemplary embodiments of three different and unique variants of the proteorhodopsin gene that were retrieved from a recombinant DNA library of other naturally occurring bacteria (i.e. the bacterial artificial chromosome library (BAC)). In general, genetic variants could be obtained from different DNA libraries containing naturally occurring bacteria as well as from samples of naturally occurring bacteria.

FIG. 6 shows the variant of the proteorhodopsin gene sequence (Sequence ID No:8) that is amplified from the BAC clone 40 (BAC40E8) with the same proteorhodopsin-

specific PCR primers as provided in Sequence ID No:2 and 3. Accordingly, FIG. 6 also shows the deduced amino acid sequence (Sequence ID No:9) of the genetic variant of proteorhodopsin shown in FIG. 6. FIG. 7 shows the variant of the proteorhodopsin gene sequence (Sequence ID No:10) that is amplified from the BAC clone 41 (BAC41B4) with the same proteorhodopsin-specific PCR primers as provided in Sequence ID No:2 and 3. Accordingly, FIG. 7 also shows the deduced amino acid sequence (Sequence ID No:11) of the genetic variant of proteorhodopsin shown in FIG. 7. FIG. 8 shows the variant of the proteorhodopsin gene sequence (Sequence ID No:12) that is amplified from the BAC clone 64 (BAC64A5) with the same proteorhodopsin-specific PCR primers as provided in Sequence ID No:2 and 3. Accordingly, FIG. 8 also shows the deduced amino acid sequence (Sequence ID No:13) of the genetic variant of proteorhodopsin shown in FIG. 8.

FIG. 9 provides a variants map of the nucleotide sequences of the proteorhodopsin gene Sequence ID No:4, Sequence ID No:8, Sequence ID No:10, and Sequence ID No:12 amplified from respectively BAC31A8, BAC40E8, BAC41B4 and BAC64A5 using the proteorhodopsin-specific PCR primers Sequence ID No:2 and Sequence ID No:3. In FIG. 9 lower case letters represent the PCR primer sequence region. Dots represent residues having identical sequence as those in Sequence ID No:4. These proteorhodopsin gene sequences differ by as much as 31 nucleotides as is shown in FIG. 10. FIG. 10 provides a variant map of the deduced amino acid sequences of the proteorhodopsin genes shown in FIG. 9.

Using the same proteorhodopsin-specific PCR primers, as for instance shown in FIGS. 2 and 3, proteorhodopsin genes were also amplified from bacterioplankton extracts. As mentioned above, any proteorhodopsin-specific PCR primer can be used. These bacterioplankton extracts include those from the Monterey Bay (referred to as MB)

clones), the Southern Ocean (Palmer Station, referred to as PAL clones), and waters of the central North Pacific Ocean (Hawaii Ocean Time series station, referred to as HOT clones).

FIGS. 11-36 show exemplary embodiments of different and unique variants of proteorhodopsin that were retrieved from the MB clones, PAL clones, and HOT clones. FIGS. 11-36 each show a variant of a proteorhodopsin gene sequence that is amplified with the same proteorhodopsin-specific PCR primers as provided in Sequence ID No:2 and Sequence ID No:3 from respectively clones HOT0m1, HOT75m1, HOT75m3, HOT75m4, HOT75m8, MB0m1, MB0m2, MB20m2, MB20m5, MB20m12, MB40m1, MB40m5, MB40m12, MB100m5, MB100m7, MB100m9, MB100m10, PALB1, PALB2, PALB5, PALB7, PALB6, PALB8, PALE1, PALE6 and PALE7. The proteorhodopsin gene sequences retrieved from clones HOT0m1, HOT75m1, HOT75m3, HOT75m4, HOT75m8, MB0m1, MB0m2, MB20m2, MB20m5, MB20m12, MB40m1, MB40m5, MB40m12, MB100m5, MB100m7, MB100m9, MB100m10, PALB1, PALB2, PALB5, PALB7, PALB6, PALB8, PALE1, PALE6 and PALE7, have respectively Sequence ID Nos: 14, 16, 18, 20, 22, 24, 26, 28, 30, 32, 34, 36, 38, 40, 42, 44, 46, 48, 50, 52, 54, 56, 58, 60, 62, and 64. Accordingly, FIGS. 11-36 also show the deduced amino acid sequence of each genetic variant of proteorhodopsin. The deduced amino acid sequence encoded by the proteorhodopsin gene retrieved from clones HOT0m1, HOT75m1, HOT75m3, HOT75m4, HOT75m8, MB0m1, MB0m2, MB20m2, MB20m5, MB20m12, MB40m1, MB40m5, MB40m12, MB100m5, MB100m7, MB100m9, MB100m10, PALB1, PALB2, PALB5, PALB7, PALB6, PALB8, PALE1, PALE6 and PALE7, have respectively Sequence ID Nos: 15, 17, 19, 21, 23, 25, 27, 29, 31, 33, 35, 37, 39, 41, 43, 45, 47, 49, 51, 53, 55, 57, 59, 61, 63, and 65.

In an exemplary embodiment shown in FIG. 37, fifteen different variants of proteorhodopsin in the PCR generated MB gene library 3710 were detected, falling into three clusters. The MB gene library includes MB clones MB0m2, MB40m5, MB20m2, MB40m12, MB100m10, MB20m12, MB40m1, MB100m5, MB20m5, MB100m7, MB0m1, and MB100m9 as well as BAC clones BAC40E8, BAC31A8 and BAC64A5. FIG. 37 is based on a phylogenetic analysis of the inferred amino acids of cloned proteorhodopsin genes. Evolutionary distances calculated from 220 positions were used to infer the tree topology by the neighbor joining method using the PaupSearch program of the Wisconsin Package version 10.0 (Genetics Computer Group (GCG), Madison Wisconsin). Other methods could also be used. The variants of the MB library share at least 97% identity over 248 amino acids, as shown in FIG. 38, and 93% identity at the DNA level. All the PCR amplified proteorhodopsin genes from Antarctic marine bacterioplankton (e.g. the PAL clones) were different from those of Monterey Bay (e.g. the MB clones) sharing 78% identity over 248 amino acids with the Monterey clade. The changes in amino acid sequences were not. restricted to the hydrophilic loops, but spread over the entire protein including changes near the retinal binding domain 3830 as shown in FIG. 38, which are predicted retinalbinding residues. FIG. 38 shows an example of a multiple alignment of proteorhodopsin amino acid sequences that were obtained from different clones 3820. The secondary structure is derived from hydropathy plots (boxes 3810 shows transmembrane helices).

### Light-driven energy generator

FIG. 39 provides a light-driven energy generator 3900 that utilizes proteorhodopsin, as obtained from naturally occurring bacteria as described above, to convert light-energy into biochemical energy. Light-driven energy generator 3900 takes advantage of the

functional properties of the proteorhodopsin protein once expressed in, for instance, E. coli and other bacteria. These properties include the ability of proteorhodopsin 3906 to integrate within the cell membrane 3904 of, for instance, E. coli making an integrated proteorhodopsin protein 3908 (also called an integrated cell membrane protein). These properties also include the ability of proteorhodopsin 3906 to bind retinal 3910, making a light absorbing pigment 3912. The source of retinal 3910 is not limited to chromophore retinal but could also include chemical derivatives of retinal, such as 3-methyl-5-(1-pyryl)-2E,4E-pentadienal, 3,7-dimethyl-9-(1-pyryl)-2E,4E,6E,8E-nonatetraenal, all-trans-9-(4-azido-2,3,5,6-tetrafluorophenyl)-3,7dimethyl-2,4,6,8,-nonatetraenal and 2,3-dehydro-4-oxoretinal. Illuminating light absorbing pigment 3912 with a light source 3914 results in a chemiosmotic gradient or proton pump in which light energy 3916 is converted into biochemical energy 3918. The chemiosmotic gradient involves pumping of protons from the inside to the outside of cell membrane 3904. When the protons return to the inside of cell membrane 3904 it produces biochemical energy 3918 via a proton translocating ATP-ase. Finally, the biochemical energy 3918 is harnessed by a mediator 3920 to produce energy 3922 for a particular process. For example, since proteorhodopsin functions as a light driven proton pump, it generates energy in the form of a proton motive force across the host cell membrane upon illumination. This light-driven proton motive force can be converted to many other forms of energy, one example above being the regeneration of adenosine triphosphate (ATP), via a proton-translocating ATPase. This coupling of the proton motive force generated by proteorhodopsin, for use by proton-translocating ATPases to synthesize ATP, could be accomplished both in living cells, as well as in artificially constructed membrane systems such as liposomes. Proteorhodopsin-based systems can convert light energy to a wide variety of useful mechanical, chemical, and electrical energy forms, for many industrial and technological applications. These

include, but are not limited to, use in targeted drug delivery, uses as primary or secondary energy generators for biocatalyic reactors, fuel cells and nano-machines (including molecular motors), as well as uses in molecular switching or data storage devices.

Applications that can potentially benefit from proteorhodopsin-light driven energy generation are, for instance, bio-electronics applications that are aimed to interface, integrate, or substitute the silicon based microelectronics systems as well as molecular devices. Other applications that can potentially benefit from proteorhodopsin-light driven energy generation are, for instance, in bio-materials, wherein proteorhodopsin is integrated as a bio-material in, for instance, optical films for light mediated computer memory applications, optical information storage and pattern recognition.

Alternatively, proteorhodopsin is useful for a process to enhance yield or increase the potential of recombinant protein production or converting the light induced membrane potential into cellular signals, including modulation of gene expression. The biochemical energy derived from functional proteorhodopsin exposed to light could be harnessed to support a variety of cellular processes. For instance, the energy derived from light-mediated proton pumping could be used to enhance the production of secondary metabolites, or recombinant proteins in host cells, such as *E. coli*. Often, production of specific compounds in the biotechnology industry is limited, since their optimal expression or production occurs in the late stationary phase of growth, when energy reserves of the host cells are low. Retinal-bound proteorhodopsin expressed in such cells would provide an ample source of biochemical energy, by simple illumination. Proteorhodopsin-mediated light driven proton production could enhance any variety of biosynthetic or physiological processes which require energy.

The biochemical energy derived from proteorhodopsin light driven proton pumping could also be converted to other generally useful energy forms, for example electricity. Microbial fuel cells currently use carbon-based compounds, such as glucose, as the primary energy source. Via specific mediators of reduction potential (e.g. electrons), these microbial fuel cells convert cellular biochemical energy to electrical potential. Unlike carbon-based microbial fuel cells, proteorhodopsin uses light as the energy source, that can then be converted into a chemiosmotic potential, and finally into cellular biochemical energy by membrane-bound proton ATP-ases. Therefore, the use of proteorhodopsin could be employed to derive energy from light as the primary or supplementary energy source, that could then be converted into electrical potential (analogous microbial fuel cells that derive their energy from glucose).

In addition to energy generation in vivo in living cells, membranes containing proteorhodopsin could be used to enhance or enable other specific processes in vitro. Polymers produced from proteorhodopsin-containing membranes may have specific properties that could be used similarly to those containing bacteriorhodopsin. One example includes the use of these light sensitive molecules for optical computing applications.

As shown in FIG. 39, the kinetics of proteorhodopsin as it is utilized in 3900 is influenced by various factors such as the type of light source 3914 and the manipulation of light source 3914 in terms of frequency and/or wavelength at which the light 3916 is delivered. Light source 3914 could be any type of light source that delivers light energy 3916 that would be absorbed by light absorbing pigment 3918.

For example, the light source 3914 could be tuned to optimally excite rhodopsin variances with an absorbance maximum of 490 nm or alternatively those rhodopsins with an absorbance maximum of 520 nm. Manipulation of the light source 3914 or the light 3916 being emitted by the light source 3914, for example, involves changing the frequency of fast-light pulses or the delivery of light 3916 as individual pulses, a train of pulses, or a continuous source of light. Manipulation also involves changing the wavelength of the delivery of light 3916 at different wavelengths. In addition, as is clear for one skilled in the art, changing the frequency and/or amount of retinal that will bind within integrated cell membrane protein 3908 also varies the function of proteorhodopsin. Finally, as was mentioned in the previous section, genetic variants of proteorhodopsin result in variants of the proteorhodopsin proteins that changes the kinetics of 3600 due to a difference in absorption of light at different wavelengths. The functional expression of such variation in these proteorhodopsin proteins adds another source of variation to the kinetics of proteorhodopsin as it is utilized in 3900.

As shown in FIG. 39, the light-driven energy generator includes a host 3902. In the present invention, as a preferred embodiment, host 3902 is a cell membrane preparation of *E. coli*. However, the present invention is not limited to the use of *E. coli* and, alternatively, other bacteria or eukaryotes could be used to provide host 3902 as an intact cell (in vivo) and/or as a cell membrane preparation (in vitro). For example, but not limited to, bacteria and yeast with developed genetic systems such as Bacillus spp. Species, Saccharomyces spp., Streptomyces spp. or Pichia spp. could be used as host for the expression of proteorhodopsin. In addition, in case a cell membrane preparation (in vitro) is used, host 3902 becomes equivalent to cell membrane 3904.

The light-driven energy generator 3900, as shown in FIG. 39, further includes proteorhodopsin 3906. Proteorhodopsin is presented in the form of the earlier presented expression vector containing a proteorhodopsin gene or one of its variants. Once proteorhodopsin 3906 has been put into host 3902, the proteorhodopsin expression vector expresses the proteorhodopsin protein in host 3902. An integral cell membrane protein 3908 is created in which the proteorhodopsin protein inserts into and folds properly within the cell membrane 3904. This is accomplished in the *E. coli* host by virtue of the native signal sequence found in the 5' end of the proteorhodopsin gene. It could also be accomplished by replacement of native sequence with another host-specific signal sequence in non-*E. coli* host systems.

As shown in FIG. 39, once retinal 3910 is added to cell membrane 3904, retinal 3910 binds within integrated cell membrane protein 3908 and forms a light absorbing pigment **3912**. The particular example of FIG. 40 shows an integrated proteorhodopsin protein 3908 bound to retinal 3910 in E. coli. Chemical derivatives of retinal (as discussed above) could also be used as a substitute chromophore to generate functional proteorhodopsin. For the particular example of FIG. 40, the proteorhodopsin protein was cloned with its native signal sequence and included an addition of the V5 epitope, and a polyhistidine tail in the C-terminus. The proteorhodopsin protein was expressed in host 3902, i.e. E. coli outer-membrane protease-deficient strain UT5600, and induced with 0.2 % arabinose for 3 hours. Cell membranes 3904 were prepared and resuspended in 50 mM Tris-Cl (pH 8.0) and 5 mM MgCl<sub>2</sub>. **FIG. 40** shows a proteorhodopsin-expressing *E.coli* cell suspension. After 3 hours of induction in the presence of 10 µM all-trans retinal, cells expressing the protein acquire a reddish pigmentation as indicated by 4010 and the + (plus) symbol. FIG. 40 also shows that a cell suspension using the same PCR primers

(Sequence ID No:2 and 3) but now in opposite orientation as a negative control, did not acquire a reddish pigmentation as indicated by 4020 and the – (minus) symbol.

FIG. 41 shows an exemplary embodiment of the absorption spectra of light absorbing pigment 3912 upon illumination with light source 3914 as is shown in FIG 39. As mentioned above, the light absorbing pigment is a retinal-reconstituted proteorhodopsin in E. coli. FIG. 41 shows absorption spectra of light absorbing pigment 3912 as well as a negative control. After retinal 3910 addition to integrated proteorhodopsin protein 3908, light absorbing pigment 3912 was made. The retinal 3910 addition was done at selected time points, i.e. 10, 20, 30 and 40 min, and shows a progression from low to high absorption values indicated by respectively 4110, 4120, 4130 and 4140 upon illumination with light source 3914. FIG. 41 also shows the absorption spectra of retinal 3910 addition at these similar time points but now to a negative control of retinal 3910 containing a proteorhodopsin 3906 that was created using the same PCR primers in opposite orientation. 4150, 4160, 4170 and 4180 indicate the four absorption spectra for the negative control. An absorption peak at 520 nm was observed after 10 minutes (4110) of incubation as illustrated in FIG. 41. On further addition of retinal, the peak at 520 nm increased, and had a ~100 nm half bandwidth. The 520 nm absorption peak was generated only in membranes containing proteorhodopsin 3906, and only in the presence of retinal 3910. The red shifted  $\lambda$ max of retinal ( $\lambda$ max = 370 nm in the free state) is indicative of a protonated Shiff base covalent linkage of retinal to proteorhodopsin.

FIG. 42 shows an exemplary embodiment of the light mediated proton pump of the light-driven energy generator 3900 indicating the conversion of light energy 3916 as shown in FIG. 39. The proton pump action is illustrated by measuring pH changes in

the medium surrounding the host 3902, which in this particular example involves a cell suspension of *E. coli*, illuminated by light source 3914. The beginning and cessation of illumination (with yellow light >485 nm delivered by 3916) is indicated 4110 ("ON") and 4120 ("OFF") respectively. The cells were suspended in 10 mM NaCl, 10 mM MgSO<sub>4</sub>·7H<sub>2</sub>O and 100 μM CaCl<sub>2</sub>. Net outward transport of protons was observed solely in proteorhodopsin-containing *E. coli* cells, and only in the presence of retinal 3910 and light 3916 and is indicated by 4210 in FIG. 42. Light-induced acidification of the medium was completely abolished by the presence of 10 μM of the protonophore CCCP.

FIG. 43 is an exemplary embodiment showing that illumination by light source 3914 generates an electrical potential at the membrane 3904 in proteorhodopsin-containing right-side-out membrane vesicles, in the presence of retinal 3910, reaching –90 mV after 2 minutes from light 3916 onset. Transport of [³H]TPP+ in *E. coli* right-side-out vesicles containing expressed proteorhodopsin, reconstituted with (4310 and 4320) or without (4330 and 4340) 10 μM retinal 3910 in the presence of light (4310 and 4330) delivered by the light source 3914 or in the dark (4320 and 4340). FIG. 43 shows that proteorhodopsin, in its form of 3912 as a light absorbing pigment, pumps protons from the inside to the outside of cell membrane in a physiologically relevant range. The ability of proteorhodopsin to generate a physiologically significant membrane potential, even when heterologously expressed in nonnative membranes, is consistent with the proton pumping function for proteorhodopsin in the native gamma proteobacteria from which it is derived.

FIG. 44 is an exemplary embodiment showing that proteorhodopsin can have a fast photocycle and can therefore be characterized as a fast and therefore efficient

transporter of protons. For the particular example of FIG. 44, light absorbing pigment 3912 is induced by laser pulses delivered by light source 3914. Laser pulse-induced absorption changes are shown by 3912 in host 3902, which in this case are suspensions of E. coli membranes containing proteorhodopsin. A 532-nm pulse (6 ns duration, 40 mJ) was delivered at time 0 and absorption changes were monitored at various wavelengths in the visible range in a lab-constructed pulse photolysis system. 64 transients were collected for each wavelength. 4410 indicates transients at 3 wavelengths exhibiting maximal amplitudes. 4420 indicates absorption difference absorption spectra calculated from amplitudes at 0.5 ms (indicated by 4430) and between 0.5 ms and 5.0 ms (indicated by 4440). In 4410, transient depletion occurred near the absorption maximum of pigment 3912 (500-nm trace indicated by 4450), and transient absorption increase was detected at 400 nm (indicated by 4460) and 590 nm (indicated by 4470), indicating a functional photocyclic reaction pathway. In 4420, the absorption difference spectrum shows that within 0.5 ms an intermediate with maximal absorption near 400 nm is produced (indicated by 4430), typical of unprotonated Schiff base forms (M intermediates) of retinylidene pigments. The 5-ms minus 0.5-ms difference spectrum 4440 shows that following M decay an intermediate species redshifted from the unphotolyzed 520-nm state appears. The decay of proteorhodopsin final intermediate is the rate limiting step in the photocycle and is fit well by a single exponential process of 15 ms, with an upward baseline shift of 13% of the initial amplitude.

As mentioned above, a proteorhodopsin gene or protein variant can be selected to determine an absorption spectra of the light absorbing pigment to change the kinetics of the light energy generator 3900, for instance to meet a design/functional criteria of an application wherein proteorhodopsin is utilized. FIG. 45 shows an exemplary

embodiment of different absorption spectra of retinal-reconstituted proteorhodopsins in *E. coli* as a function of wavelength 4510. As shown in FIG. 45, the absorbance 4520 is different and depends on the clone from which the proteorhodopsin was amplified. In this particular example, 5 µm all-trans retinal was added to the membranes suspensions in a 100 mM phosphate buffer, with a pH 7.0, and absorption spectra were recorded. The four spectra 4530, 4540, 4550, and 4560 are respectively for the proteorhodopsin genes retrieved from clones HOT75m4, PALE6, HOT0m1, and BAC31A8 at 1 hour after retinal addition. The proteorhodopsin gene retrieved from clone HOT75m4 4530 and PALE6 4540 produced a blue (490 nm) absorption maximum. The proteorhodopsin gene retrieved from clone HOT0m1 4550 and BAC31A8 4560 produced a green (527 nm) absorption maximum. In general, a range of wavelengths could be obtained that is not limited to the range shown in the example of FIG. 45.

It will be clear to one skilled in the art that the above embodiment may be altered in many ways without departing from the scope of the invention, such as for instance by mutagenesis to change the genetic sequence of proteorhodopsin and thereby changing the kinetics of the proteorhodopsin protein once it is expressed. Accordingly, the following claims and their legal equivalents should determine the scope of the invention.

#### **DEPOSITS**

Depository address: 10801 University Boulevard, Manassas, VA 20110, USA.

The Escherichia coli containing cloned DNA BAC 31A8 having assigned ATCC number PTA-3083, the Escherichia coli containing cloned DNA BAC 40E8 having assigned ATCC number PTA-3082, the Escherichia coli containing cloned DNA BAC 41B4 having assigned ATCC number PTA-3080, and the Escherichia coli containing cloned DNA BAC 64A5 having assigned ATCC number PTA-3081, all having been deposited on February 21, 2001 with the ATCC Patent Depository.

The Escherichia coli containing a plasmid PAL E6 having assigned ATCC number PTA-3250, the Escherichia coli containing a plasmid HOT 0m1 having assigned ATCC number PTA-3251, the Escherichia coli containing a plasmid HOT 75m4 having assigned ATCC number PTA-3252, and the Escherichia coli containing cloned DNA BAC64A5 having assigned ATCC number PTA 3082, all having been deposited on March 30, 2001 with the ATCC Patent Depository.

# LIGHT-DRIVEN ENERGY GENERATION USING PROTEORHODOPSIN

# LIST OF SEQUENCES THAT ARE LISTED IN THE INCORPORATED SEQUENCE LISTING

Sequence ID No:1 bacterial artificial chromosome (BAC) clone 31A8 (EBAC31A8).

Sequence ID No:2 nucleotide sequence of proteorhodopsin-specific polymerase chain reaction (PCR) primer 1.

Sequence ID No:3 nucleotide sequence of proteorhodopsin-specific polymerase chain reaction (PCR) primer 2.

Sequence ID No:4 nucleotide sequence of the proteorhodopsin gene amplified from clone EBAC31A8 (Sequence ID No. 1) using PCR primers according to Sequence ID No:2 and Sequence No:3.

Sequence ID No:5 deduced amino acid sequences of the proteorhodopsin gene amplified from clone EBAC31A8 (Sequence ID NO:4).

Sequence ID No:6 native proteorhodopsin nucleotide sequence from clone EBAC31A8 (Sequence ID No:1).

Sequence ID No:7 deduced amino acid sequences of the native proteorhodopsin nucleotide sequence from clone EBAC31A8 (Sequence ID No:6).

Sequence ID No:8 nucleotide sequence of the proteorhodopsin gene amplified from clone EBAC40E8 using PCR primers according to Sequence ID No:2 and Sequence No:3.

Sequence ID No:9 deduced amino acid sequences of the proteorhodopsin gene amplified from clone EBAC40E8 (Sequence ID NO:8).

Sequence ID No:10 nucleotide sequence of the proteorhodopsin gene amplified from clone EBAC41B4 using PCR primers according to Sequence ID No:2 and Sequence No:3.

Sequence ID No:11 deduced amino acid sequences of the proteorhodopsin gene amplified from clone EBAC41B4 (Sequence ID NO:10).

Sequence ID No:12 nucleotide sequence of the proteorhodopsin gene amplified from clone EBAC64A5 using PCR primers according to Sequence ID No:2 and Sequence No:3.

Sequence ID No:13 deduced amino acid sequences of the proteorhodopsin gene amplified from clone EBAC64A5 (Sequence ID NO:12).

Sequence ID No:14 nucleotide sequence of the proteorhodopsin gene amplified from clone HOT0m1 using PCR primers according to Sequence ID No:2 and Sequence No:3.

Sequence ID No:15 deduced amino acid sequences of the proteorhodopsin gene amplified from clone HOT0m1 (Sequence ID NO:14).

Sequence ID No:16 nucleotide sequence of the proteorhodopsin gene amplified from clone HOT75m1 using PCR primers according to Sequence ID No:2 and Sequence No:3.

Sequence ID No:17 deduced amino acid sequences of the proteorhodopsin gene amplified from clone HOT75m1 (Sequence ID NO:16).

Sequence ID No:18 nucleotide sequence of the proteorhodopsin gene amplified from clone HOT75m3 using PCR primers according to Sequence ID No:2 and Sequence No:3.

Sequence ID No:19 deduced amino acid sequences of the proteorhodopsin gene amplified from clone HOT75m3 (Sequence ID NO:18).

Sequence ID No:20 nucleotide sequence of the proteorhodopsin gene amplified from clone HOT75m4 using PCR primers according to Sequence ID No:2 and Sequence No:3.

Sequence ID No:21 deduced amino acid sequences of the proteorhodopsin gene amplified from clone HOT75m4 (Sequence ID NO:20).

Sequence ID No:22 nucleotide sequence of the proteorhodopsin gene amplified from clone HOT75m8 using PCR primers according to Sequence ID No:2 and Sequence No:3.

Sequence ID No:23 deduced amino acid sequences of the proteorhodopsin gene amplified from clone HOT75m8 (Sequence ID NO:22).

Sequence ID No:24 nucleotide sequence of the proteorhodopsin gene amplified from clone MB0m1 using PCR primers according to Sequence ID No:2 and Sequence No:3.

Sequence ID No:25 deduced amino acid sequences of the proteorhodopsin gene amplified from clone MB0m1 (Sequence ID NO:24).

Sequence ID No:26 nucleotide sequence of the proteorhodopsin gene amplified from clone MB0m2 using PCR primers according to Sequence ID No:2 and Sequence No:3.

Sequence ID No:27 deduced amino acid sequences of the proteorhodopsin gene amplified from clone MB0m2 (Sequence ID NO:26).

Sequence ID No:28 nucleotide sequence of the proteorhodopsin gene amplified from clone MB20m2 using PCR primers according to Sequence ID No:2 and Sequence No:3.

Sequence ID No:29 deduced amino acid sequences of the proteorhodopsin gene amplified from clone MB20m2 (Sequence ID NO:28).

Sequence ID No:30 nucleotide sequence of the proteorhodopsin gene amplified from clone MB20m5 using PCR primers according to Sequence ID No:2 and Sequence No:3.

Sequence ID No:31 deduced amino acid sequences of the proteorhodopsin gene amplified from clone MB20m5 (Sequence ID NO:30).

Sequence ID No:32 nucleotide sequence of the proteorhodopsin gene amplified from clone MB20m12 using PCR primers according to Sequence ID No:2 and Sequence No:3.

Sequence ID No:33 deduced amino acid sequences of the proteorhodopsin gene amplified from clone MB20m12 (Sequence ID NO:32).

Sequence ID No:34 nucleotide sequence of the proteorhodopsin gene amplified from clone MB40m1 using PCR primers according to Sequence ID No:2 and Sequence No:3.

Sequence ID No:35 deduced amino acid sequences of the proteorhodopsin gene amplified from clone MB40m1 (Sequence ID NO:34).

Sequence ID No:36 nucleotide sequence of the proteorhodopsin gene amplified from clone MB40m5 using PCR primers according to Sequence ID No:2 and Sequence No:3.

Sequence ID No:37 deduced amino acid sequences of the proteorhodopsin gene amplified from clone MB40m5 (Sequence ID NO:36).

Sequence ID No:38 nucleotide sequence of the proteorhodopsin gene amplified from clone MB40m12 using PCR primers according to Sequence ID No:2 and Sequence No:3.

Sequence ID No:39 deduced amino acid sequences of the proteorhodopsin gene amplified from clone MB40m12 (Sequence ID NO:38).

Sequence ID No:40 nucleotide sequence of the proteorhodopsin gene amplified from clone MB100m5 using PCR primers according to Sequence ID No:2 and Sequence No:3.

Sequence ID No:41 deduced amino acid sequences of the proteorhodopsin gene amplified from clone MB100m5 (Sequence ID NO:40).

Sequence ID No:42 nucleotide sequence of the proteorhodopsin gene amplified from clone MB100m7 using PCR primers according to Sequence ID No:2 and Sequence No:3.

Sequence ID No:43 deduced amino acid sequences of the proteorhodopsin gene amplified from clone MB100m7 (Sequence ID NO:42).

Sequence ID No:44 nucleotide sequence of the proteorhodopsin gene amplified from clone MB100m9 using PCR primers according to Sequence ID No:2 and Sequence No:3.

Sequence ID No:45 deduced amino acid sequences of the proteorhodopsin gene amplified from clone MB100m9 (Sequence ID NO:44).

Sequence ID No:46 nucleotide sequence of the proteorhodopsin gene amplified from clone MB100m10 using PCR primers according to Sequence ID No:2 and Sequence No:3.

Sequence ID No:47 deduced amino acid sequences of the proteorhodopsin gene amplified from clone MB100m10 (Sequence ID NO:46).

Sequence ID No:48 nucleotide sequence of the proteorhodopsin gene amplified from clone PALB1 using PCR primers according to Sequence ID No:2 and Sequence No:3.

Sequence ID No:49 deduced amino acid sequences of the proteorhodopsin gene amplified from clone PALB1 (Sequence ID NO:48).

Sequence ID No:50 nucleotide sequence of the proteorhodopsin gene amplified from clone PALB2 using PCR primers according to Sequence ID No:2 and Sequence No:3.

Sequence ID No:51 deduced amino acid sequences of the proteorhodopsin gene amplified from clone PALB2 (Sequence ID NO:50).

Sequence ID No:52 nucleotide sequence of the proteorhodopsin gene amplified from clone PALB5 using PCR primers according to Sequence ID No:2 and Sequence No:3.

Sequence ID No:53 deduced amino acid sequences of the proteorhodopsin gene amplified from clone PALB5 (Sequence ID NO:52).

Sequence ID No:54 nucleotide sequence of the proteorhodopsin gene amplified from clone PALB7 using PCR primers according to Sequence ID No:2 and Sequence No:3.

Sequence ID No:55 deduced amino acid sequences of the proteorhodopsin gene amplified from clone PALB7 (Sequence ID NO:54).

Sequence ID No:56 nucleotide sequence of the proteorhodopsin gene amplified from clone PALB6 using PCR primers according to Sequence ID No:2 and Sequence No:3.

Sequence ID No:57 deduced amino acid sequences of the proteorhodopsin gene amplified from clone PALB6 (Sequence ID NO:56).

Sequence ID No:58 nucleotide sequence of the proteorhodopsin gene amplified from clone PALB8 using PCR primers according to Sequence ID No:2 and Sequence No:3.

Sequence ID No:59 deduced amino acid sequences of the proteorhodopsin gene amplified from clone PALB8 (Sequence ID NO:58).

Sequence ID No:60 nucleotide sequence of the proteorhodopsin gene amplified from clone PALE1 using PCR primers according to Sequence ID No:2 and Sequence No:3.

Sequence ID No:61 deduced amino acid sequences of the proteorhodopsin gene amplified from clone PALE1 (Sequence ID NO:60).

Sequence ID No:62 nucleotide sequence of the proteorhodopsin gene amplified from clone PALE6 using PCR primers according to Sequence ID No:2 and Sequence No:3.

Sequence ID No:63 deduced amino acid sequences of the proteorhodopsin gene amplified from clone PALE6 (Sequence ID NO:62).

Sequence ID No:64 nucleotide sequence of the proteorhodopsin gene amplified from clone PALE7 using PCR primers according to Sequence ID No:2 and Sequence No:3.

Sequence ID No:65 deduced amino acid sequences of the proteorhodopsin gene amplified from clone PALE7 (Sequence ID NO:64).

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	tte Leks					
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09	attagtttat	ctaatatata	taacttaata	attgctccaa	ttgttatatc agtaatggct	ttgttatatc

teceaaaaga ttaaccatet ttgactgate aactatacat ataaactegt tagaggeaga

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1620	gaaataaaaa	aacaactcca	ttatgccaat	tgcttgatag	aaaaattaat	gtaagaaatt
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1380	acatttgctc	atcacctata	tagcattaaa	gtttatgacg	taatgcatct	agcttattcc
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1740	catccttttg	gtcttttgtt	aaaaaaatt	attgcaaaga	ggcactgttt	cattaaaaga	

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8220 8280 8340 8400	aaaaattgct cgttgatatt atttgcactt gtcaataaaa	caaatattgc taacttttgt aaaaaggaat cagtggtttg	ggaagaaatt caaacagctt gttttttctg aataaatgca	tggatgtgat tgactactta agctcaccaa gggtgagatg	ataaaaacga atctaattgc tcacttacaa gcagcttcga gataatgatt cacatggcaa atgccactcc cagaaggcaa	ataaaaacga tcacttacaa gataatgatt atgccactcc
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APPENDIX

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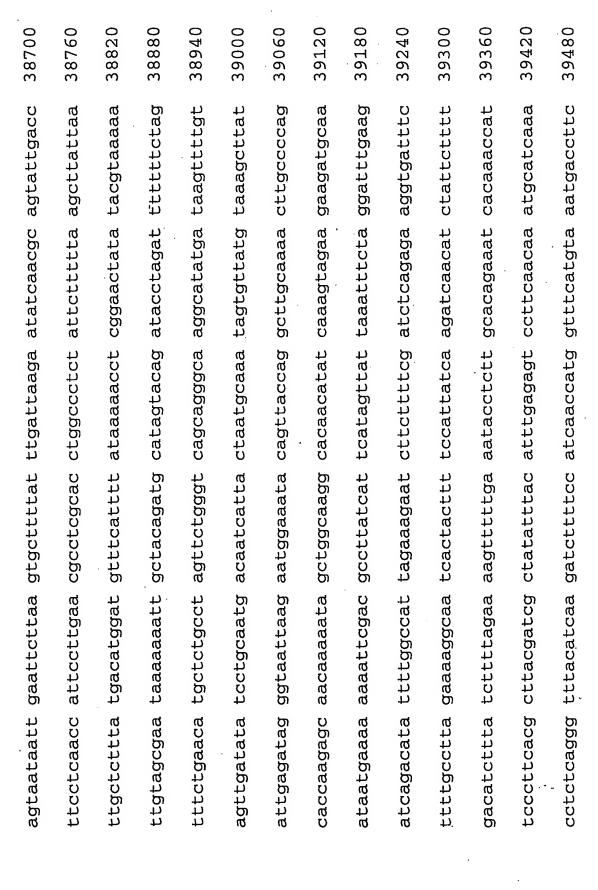
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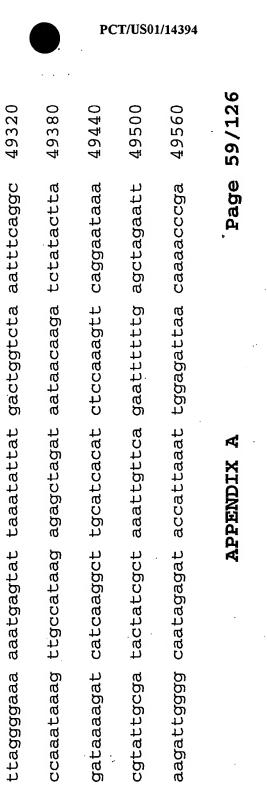
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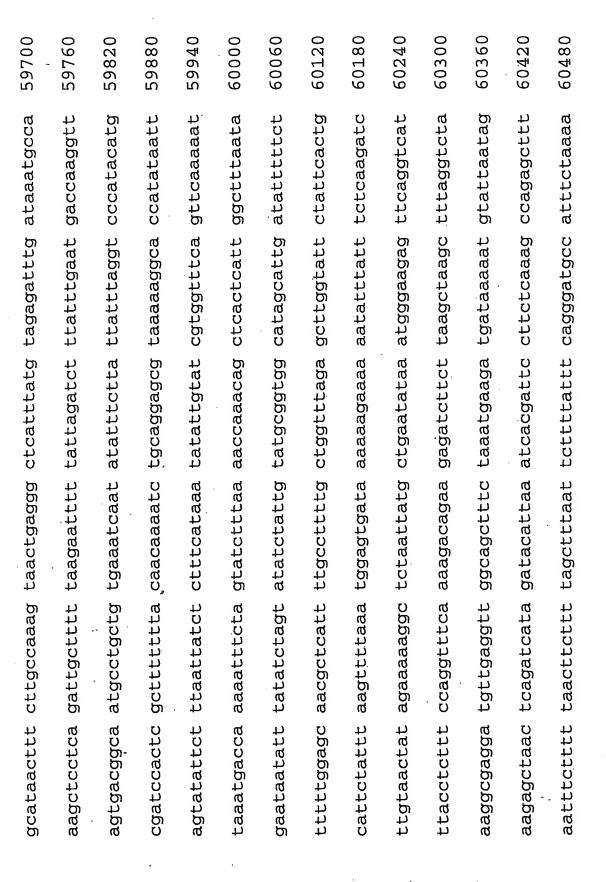
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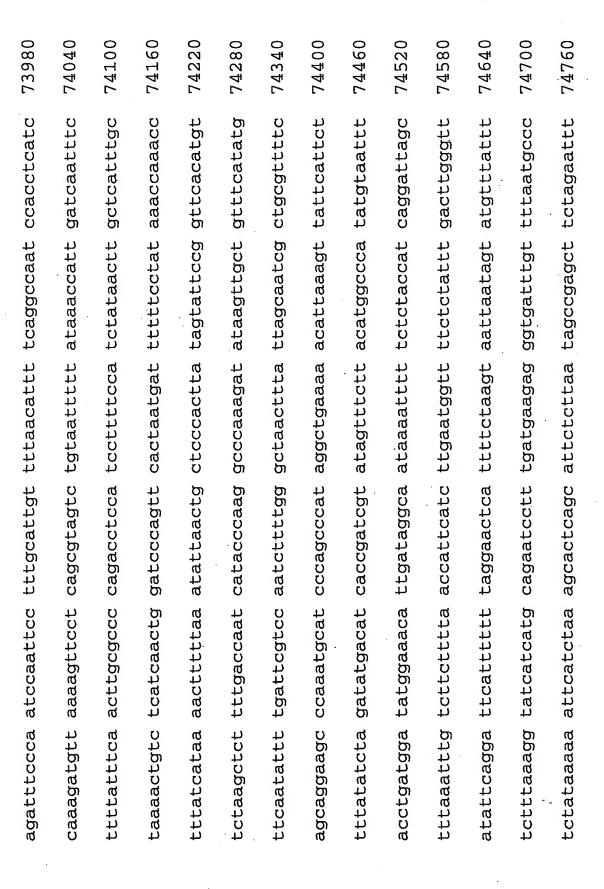
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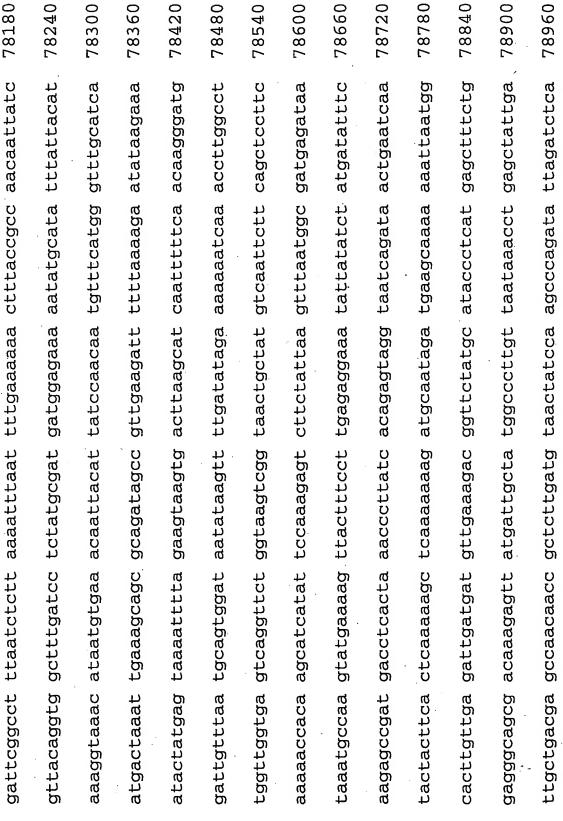
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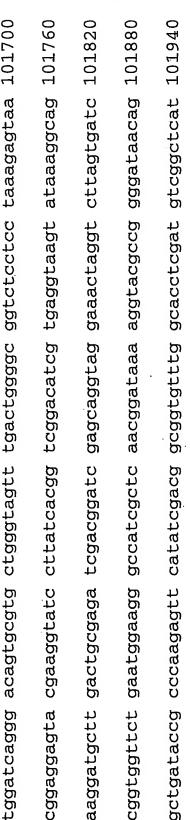
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MBA-101





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4 APPENDIX

MBA-101

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APPENDIX A

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## **CLAIMS**

## What is claimed is:

- 1. A proteorhodopsin gene, comprising an isolated DNA sequence for encoding a proteorhodopsin protein.
  - 2. The proteorhodopsin gene of claim 1, wherein said proteorhodopsin gene is retrieved from a genomic fragment of a sample of naturally occurring bacteria.
    - 3. The proteorhodopsin gene of claim 2, wherein said naturally occurring bacteria are marine proteobacteria.
    - 4. The proteorhodopsin gene of claim 2, wherein said naturally occurring bacteria are SAR86 bacteria.
    - The proteorhodopsin gene of claim 2, wherein said naturally occurring bacterial genomic fragment is retrieved from a recombinant DNA library.
      - 6. The proteorhodopsin gene of claim 5, wherein said naturally occurring bacterial genomic fragment is retrieved from a bacterial artificial chromosome library.

- 7: The proteorhodopsin gene of claim 2, wherein said genomic fragment is retrieved from a clone BAC31A8, said proteorhodopsin gene is Sequence ID No:4 and said proteorhodopsin protein is Sequence ID No:5.
- 8. The proteorhodopsin gene of claim 2, wherein said genomic fragment is retrieved from a clone BAC40E8, said proteorhodopsin gene is Sequence ID No:8 and said proteorhodopsin protein is Sequence ID No:9.
- 9. The proteorhodopsin gene of claim 2, wherein said genomic fragment is retrieved from a clone BAC41B4, said proteorhodopsin gene is Sequence ID No:10 and said proteorhodopsin protein is Sequence ID No:11.
- 10. The proteorhodopsin gene of claim 2, wherein said genomic fragment is retrieved from a clone BAC64A5, said proteorhodopsin gene is Sequence ID No:12 and said proteorhodopsin protein is Sequence ID No:13.
- 11. The proteorhodopsin gene of claim 2, wherein said genomic fragment is retrieved from a clone HOT0m1, said proteorhodopsin gene is Sequence ID No:14 and said proteorhodopsin protein is Sequence ID No:15.

- 12. The proteorhodopsin gene of claim 2, wherein said genomic fragment is retrieved from a clone HOT75m1, said proteorhodopsin gene is Sequence ID No:16 and said proteorhodopsin protein is Sequence ID No:17.
- 13. The proteorhodopsin gene of claim 2, wherein said genomic fragment is retrieved from a clone HOT75m3, said proteorhodopsin gene is Sequence ID No:18 and said proteorhodopsin protein is Sequence ID No:19.
- 14. The proteorhodopsin gene of claim 2, wherein said genomic fragment is retrieved from a clone HOT75m4, said proteorhodopsin gene is Sequence ID No:20 and said proteorhodopsin protein is Sequence ID No:21.
- 15. The proteorhodopsin gene of claim 2, wherein said genomic fragment is retrieved from a clone HOT75m8, said proteorhodopsin gene is Sequence ID No:22 and said proteorhodopsin protein is Sequence ID No:23.
- 16. The proteorhodopsin gene of claim 2, wherein said genomic fragment is retrieved from a clone MB0m1, said proteorhodopsin gene is Sequence ID No:24 and said proteorhodopsin protein is Sequence ID No:25.

- 17. The proteorhodopsin gene of claim 2, wherein said genomic fragment is retrieved from a clone MB0m2, said proteorhodopsin gene is Sequence ID No:26 and said proteorhodopsin protein is Sequence ID No:27.
- 18. The proteorhodopsin gene of claim 2, wherein said genomic fragment is retrieved from a clone MB20m2, said proteorhodopsin gene is Sequence ID No:28 and said proteorhodopsin protein is Sequence ID No:29.
- 19. The proteorhodopsin gene of claim 2, wherein said genomic fragment is retrieved from a clone MB20m5, said proteorhodopsin gene is Sequence ID No:30 and said proteorhodopsin protein is Sequence ID No:31.
- 20. The proteorhodopsin gene of claim 2, wherein said genomic fragment is retrieved from a clone MB20m12, said proteorhodopsin gene is Sequence ID No:32 and said proteorhodopsin protein is Sequence ID No:33.
- 21. The proteorhodopsin gene of claim 2, wherein said genomic fragment is retrieved from a clone MB40m1, said proteorhodopsin gene is Sequence ID No:34 and said proteorhodopsin protein is Sequence ID No:35.

- 22. The proteorhodopsin gene of claim 2, wherein said genomic fragment is retrieved from a clone MB40m5, said proteorhodopsin gene is Sequence ID No:36 and said proteorhodopsin protein is Sequence ID No:37.
- 23. The proteorhodopsin gene of claim 2, wherein said genomic fragment is retrieved from a clone MB40m12, said proteorhodopsin gene is Sequence ID No:38 and said proteorhodopsin protein is Sequence ID No:39.
- 24. The proteorhodopsin gene of claim 2, wherein said genomic fragment is retrieved from a clone MB100m5, said proteorhodopsin gene is Sequence ID No:40 and said proteorhodopsin protein is Sequence ID No:41.
- 25. The proteorhodopsin gene of claim 2, wherein said genomic fragment is retrieved from a clone MB100m7, said proteorhodopsin gene is Sequence ID No:42 and said proteorhodopsin protein is Sequence ID No:43.
- 26. The proteorhodopsin gene of claim 2, wherein said genomic fragment is retrieved from a clone MB100m9, said proteorhodopsin gene is Sequence ID No:44 and said proteorhodopsin protein is Sequence ID No:45.

- 27. The proteorhodopsin gene of claim 2, wherein said genomic fragment is retrieved from a clone MB100m10, said proteorhodopsin gene is Sequence ID No:46 and said proteorhodopsin protein is Sequence ID No:47.
- 28. The proteorhodopsin gene of claim 2, wherein said genomic fragment is retrieved from a clone PALB1, said proteorhodopsin gene is Sequence ID No:48 and said proteorhodopsin protein is Sequence ID No:49.
- 29. The proteorhodopsin gene of claim 2, wherein said genomic fragment is retrieved from a clone PALB2, said proteorhodopsin gene is Sequence ID No:50 and said proteorhodopsin protein is Sequence ID No:51.
- 30. The proteorhodopsin gene of claim 2, wherein said genomic fragment is retrieved from a clone PALB5, said proteorhodopsin gene is Sequence ID No:52 and said proteorhodopsin protein is Sequence ID No:53.
- 31. The proteorhodopsin gene of claim 2, wherein said genomic fragment is retrieved from a clone PALB7, said proteorhodopsin gene is Sequence ID No:54 and said proteorhodopsin protein is Sequence ID No:55.

- 32. The proteorhodopsin gene of claim 2, wherein said genomic fragment is retrieved from a clone PALB6, said proteorhodopsin gene is Sequence ID No:56 and said proteorhodopsin protein is Sequence ID No:57.
- 33. The proteorhodopsin gene of claim 2, wherein said genomic fragment is retrieved from a clone PALB8, said proteorhodopsin gene is Sequence ID No:58 and said proteorhodopsin protein is Sequence ID No:59.
- 34. The proteorhodopsin gene of claim 2, wherein said genomic fragment is retrieved from a clone PALE1, said proteorhodopsin gene is Sequence ID No:60 and said proteorhodopsin protein is Sequence ID No:61.
- 35. The proteorhodopsin gene of claim 2, wherein said genomic fragment is retrieved from a clone PALE6, said proteorhodopsin gene is Sequence ID No:62 and said proteorhodopsin protein is Sequence ID No:63.
- 36. The proteorhodopsin gene of claim 2, wherein said genomic fragment is retrieved from a clone PALE7, said proteorhodopsin gene is Sequence ID No:64 and said proteorhodopsin protein is Sequence ID No:65.

- 37. The proteorhodopsin gene of claim 1, wherein said proteorhodopsin gene is amplified from a genomic fragment by polymerase chain reaction.
  - 38. The proteorhodopsin gene of claim 37, wherein said polymerase chain reaction is performed by primers with Sequence ID No:2 and Sequence ID No:3.
- 39. The proteorhodopsin gene of claim 1, wherein said proteorhodopsin gene is derived from a marine environment and placed in an expression vector for producing said proteorhodopsin protein in a host.
  - 40. The proteorhodopsin gene of claim 39, wherein said host is an artificial membrane system.
  - 41. The proteorhodopsin gene of claim 39, wherein said host is a bacterium.
    - 42. The proteorhodopsin gene of claim 41, wherein said host is a cell membrane preparation of said bacterium.
  - 43. The proteorhodopsin gene of claim 39, wherein said host is an eukaryote.
    - 44. The proteorhodopsin gene of claim 43, wherein said host is a cell membrane preparation of said eukaryote.

- 45. A method of retrieving a proteorhodopsin gene, comprising the steps of:
  - (a) providing a sample of naturally occurring bacteria;
  - (b) extracting a genomic fragment of said sample of naturally occurring bacteria; and
  - (c) amplifying said proteorhodopsin gene from said genomic fragment using polymerase chain reaction.
  - 46. The method of claim 45, further comprising the step of creating an expression vector containing said proteorhodopsin gene.
  - 47. The method of claim 45, wherein said naturally occurring bacteria are marine proteobacteria.
  - 48. The method of claim 45, wherein said naturally occurring bacteria are SAR86 bacteria.
  - 49. The method of claim 45, wherein said naturally occurring bacterial genomic fragment is retrieved from a recombinant DNA library.
    - 50. The method of claim 49, said naturally occurring bacterial genomic fragment is retrieved from a bacterial artificial chromosome library.
  - 51. The method of claim 45, wherein said naturally occurring bacterial genomic fragment is in a clone BAC31A8, and wherein said amplified

- proteorhodopsin gene from said clone BAC31A8 is Sequence ID No:4 and encodes a proteorhodopsin protein according to Sequence ID No:5.
- 52. The method of claim 45, wherein said naturally occurring bacterial genomic fragment is in a clone BAC40E8, and wherein said amplified proteorhodopsin gene from said clone BAC40E8 is Sequence ID No:8 and encodes a proteorhodopsin protein according to Sequence ID No:9.
- 53. The method of claim 45, wherein said naturally occurring bacterial genomic fragment is in a clone BAC41B4, and wherein said amplified proteorhodopsin gene from said clone BAC41B4 is Sequence ID No:10 and encodes a proteorhodopsin protein according to Sequence ID No:11.
- 54. The method of claim 45, wherein said naturally occurring bacterial genomic fragment is in a clone BAC64A5, and wherein said amplified proteorhodopsin gene from said clone BAC64A5 is Sequence ID No:12 and encodes a proteorhodopsin protein according to Sequence ID No:13.
- 55. The method of claim 45, wherein said naturally occurring bacterial genomic fragment is in a clone HOT0m1, and wherein said amplified proteorhodopsin gene from said clone HOT0m1 is Sequence ID No:14 and encodes a proteorhodopsin protein according to Sequence ID No:15.
- 56. The method of claim 45, wherein said naturally occurring bacterial genomic fragment is in a clone HOT75m1, and wherein said amplified

proteorhodopsin gene from said clone HOT75m1 is Sequence ID No:16 and encodes a proteorhodopsin protein according to Sequence ID No:17.

- 57. The method of claim 45, wherein said naturally occurring bacterial genomic fragment is in a clone HOT75m3, and wherein said amplified proteorhodopsin gene from said clone HOT75m3 is Sequence ID No:18 and encodes a proteorhodopsin protein according to Sequence ID No:19.
- 58. The method of claim 45, wherein said naturally occurring bacterial genomic fragment is in a clone HOT75m4, and wherein said amplified proteorhodopsin gene from said clone HOT75m4 is Sequence ID No:20 and encodes a proteorhodopsin protein according to Sequence ID No:21.
- 59. The method of claim 45, wherein said naturally occurring bacterial genomic fragment is in a clone HOT75m8, and wherein said amplified proteorhodopsin gene from said clone HOT75m8 is Sequence ID No:22 and encodes a proteorhodopsin protein according to Sequence ID No:23.
- 60. The method of claim 45, wherein said naturally occurring bacterial genomic fragment is in a clone MB0m1, and wherein said amplified proteorhodopsin gene from said clone MB0m1 is Sequence ID No:24 and encodes a proteorhodopsin protein according to Sequence ID No:25.
- 61. The method of claim 45, wherein said naturally occurring bacterial genomic fragment is in a clone MB0m2, and wherein said amplified

proteorhodopsin gene from said clone MB0m2 is Sequence ID No:26 and encodes a proteorhodopsin protein according to Sequence ID No:27.

- 62. The method of claim 45, wherein said naturally occurring bacterial genomic fragment is in a clone MB20m2, and wherein said amplified proteorhodopsin gene from said clone MB20m2 is Sequence ID No:28 and encodes a proteorhodopsin protein according to Sequence ID No:29.
- 63. The method of claim 45, wherein said naturally occurring bacterial genomic fragment is in a clone MB20m5, and wherein said amplified proteorhodopsin gene from said clone MB20m5 is Sequence ID No:30 and encodes a proteorhodopsin protein according to Sequence ID No:31.
- 64. The method of claim 45, wherein said naturally occurring bacterial genomic fragment is in a clone MB20m12, and wherein said amplified proteorhodopsin gene from said clone MB20m12 is Sequence ID No:32 and encodes a proteorhodopsin protein according to Sequence ID No:33.
- 65. The method of claim 45, wherein said naturally occurring bacterial genomic fragment is in a clone MB40m1, and wherein said amplified proteorhodopsin gene from said clone MB40m1 is Sequence ID No:34 and encodes a proteorhodopsin protein according to Sequence ID No:35.
- 66. The method of claim 45, wherein said naturally occurring bacterial genomic fragment is in a clone MB40m5, and wherein said amplified

proteorhodopsin gene from said clone MB40m5 is Sequence ID No:36 and encodes a proteorhodopsin protein according to Sequence ID No:37.

- 67. The method of claim 45, wherein said naturally occurring bacterial genomic fragment is in a clone MB40m12, and wherein said amplified proteorhodopsin gene from said clone MB40m12 is Sequence ID No:38 and encodes a proteorhodopsin protein according to Sequence ID No:39.
- 68. The method of claim 45, wherein said naturally occurring bacterial genomic fragment is in a clone MB100m5, and wherein said amplified proteorhodopsin gene from said clone MB100m5 is Sequence ID No:40 and encodes a proteorhodopsin protein according to Sequence ID No:41.
- 69. The method of claim 45, wherein said naturally occurring bacterial genomic fragment is in a clone MB100m7, and wherein said amplified proteorhodopsin gene from said clone MB100m7 is Sequence ID No:42 and encodes a proteorhodopsin protein according to Sequence ID No:43.
- 70. The method of claim 45, wherein said naturally occurring bacterial genomic fragment is in a clone MB100m9, and wherein said amplified proteorhodopsin gene from said clone MB100m9 is Sequence ID No:44 and encodes a proteorhodopsin protein according to Sequence ID No:45.
- 71. The method of claim 45, wherein said naturally occurring bacterial genomic fragment is in a clone MB100m10, and wherein said amplified

proteorhodopsin gene from said clone MB100m10 is Sequence ID No:46 and encodes a proteorhodopsin protein according to Sequence ID No:47.

- 72. The method of claim 45, wherein said naturally occurring bacterial genomic fragment is in a clone PALB1, and wherein said amplified proteorhodopsin gene from said clone PALB1 is Sequence ID No:48 and encodes a proteorhodopsin protein according to Sequence ID No:49.
- 73. The method of claim 45, wherein said naturally occurring bacterial genomic fragment is in a clone PALB2, and wherein said amplified proteorhodopsin gene from said clone PALB2 is Sequence ID No:50 and encodes a proteorhodopsin protein according to Sequence ID No:51.
- 74. The method of claim 45, wherein said naturally occurring bacterial genomic fragment is in a clone PALB5, and wherein said amplified proteorhodopsin gene from said clone PALB5 is Sequence ID No:52 and encodes a proteorhodopsin protein according to Sequence ID No:53.
- 75. The method of claim 45, wherein said naturally occurring bacterial genomic fragment is in a clone PALB7, and wherein said amplified proteorhodopsin gene from said clone PALB7 is Sequence ID No:54 and encodes a proteorhodopsin protein according to Sequence ID No:55.
- 76. The method of claim 45, wherein said naturally occurring bacterial genomic fragment is in a clone PALB6, and wherein said amplified

proteorhodopsin gene from said clone PALB6 is Sequence ID No:56 and encodes a proteorhodopsin protein according to Sequence ID No:57.

- 77. The method of claim 45, wherein said naturally occurring bacterial genomic fragment is in a clone PALB8, and wherein said amplified proteorhodopsin gene from said clone PALB8 is Sequence ID No:58 and encodes a proteorhodopsin protein according to Sequence ID No:59.
- 78. The method of claim 45, wherein said naturally occurring bacterial genomic fragment is in a clone PALE1, and wherein said amplified proteorhodopsin gene from said clone PALE1 is Sequence ID No:60 and encodes a proteorhodopsin protein according to Sequence ID No:61.
- 79. The method of claim 45, wherein said naturally occurring bacterial genomic fragment is in a clone PALE6, and wherein said amplified proteorhodopsin gene from said clone PALE6 is Sequence ID No:62 and encodes a proteorhodopsin protein according to Sequence ID No:63.
- 80. The method of claim 45, wherein said naturally occurring bacterial genomic fragment is in a clone PALE7, and wherein said amplified proteorhodopsin gene from said clone PALE7 is Sequence ID No:64 and encodes a proteorhodopsin protein according to Sequence ID No:65.
- 81. The method of claim 45, wherein said polymerase chain reaction is performed by primers with Sequence ID No:2 and Sequence ID No:3.

- 82. The method of claim 45, further comprising the step of providing a host.
  - 83. The method of claim 82, wherein said host is an artificial membrane system.
  - 84. The method of claim 82, wherein said host is a bacterium.
    - 85. The method of claim 84, wherein said host is a cell membrane preparation of said bacterium.
  - 86. The method of claim 82, wherein said host is an eukaryote.
    - 87. The method of claim 86, wherein said host is a cell membrane preparation of said eukaryote.
- 88. A light-driven energy generator, comprising:
  - (a) a proteorhodopsin protein;
  - (b) a host to correctly fold said proteorhodopsin protein in said host, thereby creating an integrated proteorhodopsin protein; and
  - (c) a source of retinal to bind covalently to said integrated proteorhodopsin protein, thereby creating a light absorbing pigment.
  - 89. The light-driven energy generator of claim 88, wherein said proteorhodopsin protein is encoded by a proteorhodopsin gene retrieved from a genomic fragment of a sample of naturally occurring bacteria.

- 90. The light-driven energy generator of claim 89, wherein said naturally occurring bacteria are marine proteobacteria.
- 91. The light-driven energy generator of claim 89, wherein said naturally occurring bacteria are SAR86 bacteria.
- 92. The light-driven energy generator of claim 89, wherein said naturally occurring bacterial genomic fragment is retrieved from a recombinant DNA library.
  - 93. The light-driven energy generator of claim 92, wherein said naturally occurring bacterial genomic fragment is retrieved from a bacterial artificial chromosome library.
- 94. The light-driven energy generator of claim 89, wherein said genomic fragment is retrieved from a clone, wherein said clone is a member of the group consisting of BAC31A8, BAC40E8, BAC41B4, BAC64A5, HOT0m1, HOT75m1, HOT75m3, HOT75m4, HOT75m8, MB0m1, MB0m2, MB20m2, MB20m5, MB20m12, MB40m1, MB40m5, MB40m12, MB100m5, MB100m7, MB100m9, MB100m10, PALB1, PALB2, PALB5, PALB7, PALB6, PALB8, PALE1, PALE6 and PALE7.
- 95. The light-driven energy generator of claim 88, wherein said host is an artificial membrane system.

- 96. The light-driven energy generator of claim 88, wherein said host is a cell membrane obtained from a bacterium.
  - 97. The light-driven energy generator of claim 96, wherein said host is a cell membrane preparation obtained from a bacterium.
- 98. The light-driven energy generator of claim 88, wherein said host is a cell membrane obtained from an eukaryote.
  - 99. The light-driven energy generator of claim 98, wherein said host is a cell membrane preparation obtained from an eukaryote.
- 100. The light-driven energy generator of claim 88, further comprising a light source for illuminating said light absorbing pigment, whereby said energy generator converts light into biochemical energy.
  - 101. The light-driven energy generator of claim 100, wherein said light source is a fast-pulsed light source.
    - 102. The light-driven energy generator of claim 101, wherein said fast-pulsed light source comprises a mechanism for delivering intermittant fast-light pulses at predetermined time intervals.

- 103. The light-driven energy generator of claim 100, wherein said light source is a light source exhibiting different predetermined wavelengths.
- 104. The light-driven energy generator of claim 88, further comprising a mediator for mediating energy generated by said energy generator into chemical, mechanical or electrical energy.
- 105. The light-driven energy generator of claim 88, wherein said proteorhodopsin protein is selected to determine an absorption spectra of said light absorbing pigment.
- 106. A method for making a light-driven energy generator, comprising the steps of:
  - (a) providing a proteorhodopsin protein;
  - (b) providing a host to correctly fold said proteorhodopsin protein in said host, thereby creating an integrated proteorhodopsin protein; and
  - (c) providing a source of retinal to bind covalently to said integrated proteorhodopsin protein, thereby creating a light absorbing pigment.
  - 107. The method of claim 106, wherein said proteorhodopsin protein is encoded by a proteorhodopsin gene retrieved from a genomic fragment of a sample of naturally occurring bacteria.
    - 108. The method of claim 107, wherein said naturally occurring bacteria are marine proteobacteria.

- 109. The method of claim 107, wherein said naturally occurring bacteria are SAR86 bacteria.
- 110. The method of claim 107, wherein said naturally occurring bacterial genomic fragment is retrieved from a recombinant DNA library.
  - 111. The method of claim 110, wherein said naturally occurring bacterial genomic fragment is retrieved from a bacterial artificial chromosome library.
- 112. The method of claim 107, wherein said genomic fragment is retrieved from a clone, wherein said clone is a member of the group consisting of BAC31A8, BAC40E8, BAC41B4, BAC64A5, HOT0m1, HOT75m1, HOT75m3, HOT75m4, HOT75m8, MB0m1, MB0m2, MB20m2, MB20m5, MB20m12, MB40m1, MB40m5, MB40m12, MB100m5, MB100m7, MB100m9, MB100m10, PALB1, PALB2, PALB5, PALB7, PALB6, PALB8, PALE1, PALE6 and PALE7.
- 113. The method of claim 106, wherein said host is an artificial membrane system.
- 114. The method of claim 106, wherein said host is a cell membrane obtained from a bacterium.

- 115. The method of claim 114, wherein said host is a cell membrane preparation obtained from a bacterium.
- 116. The method of claim 106, wherein said host is a cell membrane obtained from an eukaryote.
  - 117. The method of claim 116, wherein said host is a cell membrane preparation obtained from an eukaryote.
- 118. The method of claim 106, further comprising the step of providing a light source for illuminating said light absorbing pigment, whereby said energy generator converts light into biochemical energy.
  - 119. The method of claim 118, wherein said light source is a fast-pulsed light source.
    - 120. The method of claim 119, wherein said fast-pulsed light source comprises a mechanism for delivering intermittant fast-light pulses at predetermined time intervals.
  - 121. The method of claim 118, wherein said light source is a light source exhibiting different predetermined wavelengths.
- 122. The method of claim 106, further comprising the step of providing a mediator for mediating energy generated by said energy generator into chemical, mechanical or electrical energy.

- 123. The method of claim 106, wherein said proteorhodopsin protein is selected to determine an absorption spectra of said light absorbing pigment.
- 124. A PCR apparatus for amplifying a proteorhodopsin gene from DNA samples of naturally occurring microbial populations using polymerase chain reaction, comprising oligodeoxynucleotide primers with a Watson-Crick base pair complementarity to 5' and 3' ends of said proteorhodopsin gene.
  - 125. The apparatus of claim 124, wherein said primers are according to Sequence ID No:2 and Sequence ID No:3.
- 126. A method of designing PCR primers, comprising the steps of:
  - (a) determining a DNA sequence of a proteorhodopsin gene; and
  - (b) based on said determined DNA sequence in (a), designing oligodeoxynucleotide primers with a Watson-Crick base pair complementarity to said 5' and 3' ends of said proteorhodopsin gene.
  - 127. The method of claim 126, further comprising the step of using said oligodeoxynucleotide primers to amplify said proteorhodopsin gene from DNA samples of naturally occurring microbial populations by polymerase chain reaction.
    - 128. The method of claim 127, further comprising the step of cloning said amplified proteorhodopsin gene into an expression vector.

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129. The method of claim 126, wherein said primers are according to Sequence ID No:2 and Sequence ID No:3.

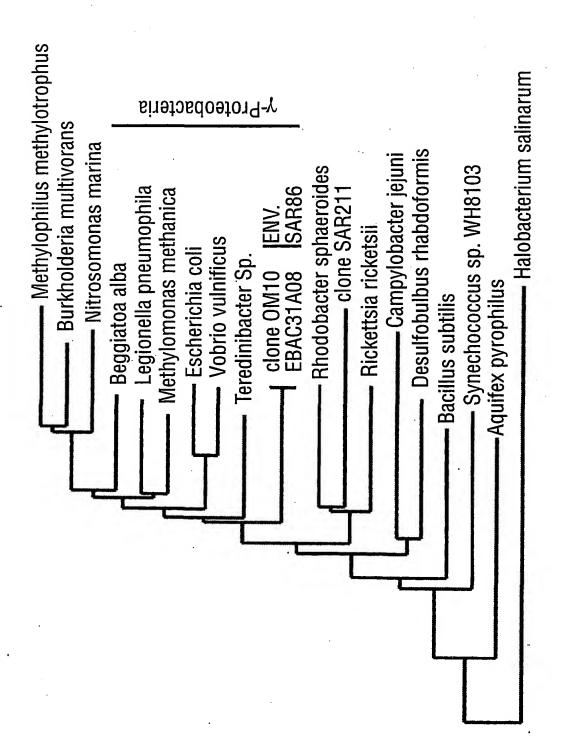


Fig. 1

accatgggta aattattact gatattagg

igure :

gattctttaa agcattagaa

48	96	144	192	240	288	336
aaa tta tta ctg ata tta ggt agt gtt att gca ctt cct aca	gca ggt ggt gac ctt gat gct agt gat tac act ggt gtt	tgg tta gtt act gct gtt tta tta gca tct act gta ttt ttc	gaa aga gat aga gtt tct gca aaa tgg aaa aca tca tta act	ggt ctt gtt act ggt att gct ttc tgg cat tac atg tac atg	gta tgg att gaa act ggt gat tcg cca act gta ttt aga tac	tgg tta cta aca gtt cct cta tta ata tgt gaa ttc tac tta
Lys Leu Leu Ile Leu Gly Ser Val Ile Ala Leu Pro Thr	Ala Gly Gly Asp Leu Asp Ala Ser Asp Tyr Thr Gly Val	Trp Leu Val Thr Ala Ala Leu Leu Ala Ser Thr Val Phe Phe	Glu Arg Asp Arg Val Ser Ala Lys Trp Lys Thr Ser Leu Thr	Gly Leu Val Thr Gly Ile Ala Phe Trp His Tyr Met Tyr Met	Val Trp Ile Glu Thr Gly Asp Ser Pro Thr Val Phe Arg Tyr	Trp Leu Leu Thr Val Pro Leu Leu Ile Cys Glu Phe Tyr Leu
5	20	35	55	70	90	100
atg ggt	ttt gct	ser phe	ttt gtt g	gta tct g	aga ggg g	att gat t
Met Gly 1	Phe Ala		Phe Val (	Val Ser (	Arg Gly V	Ile Asp :

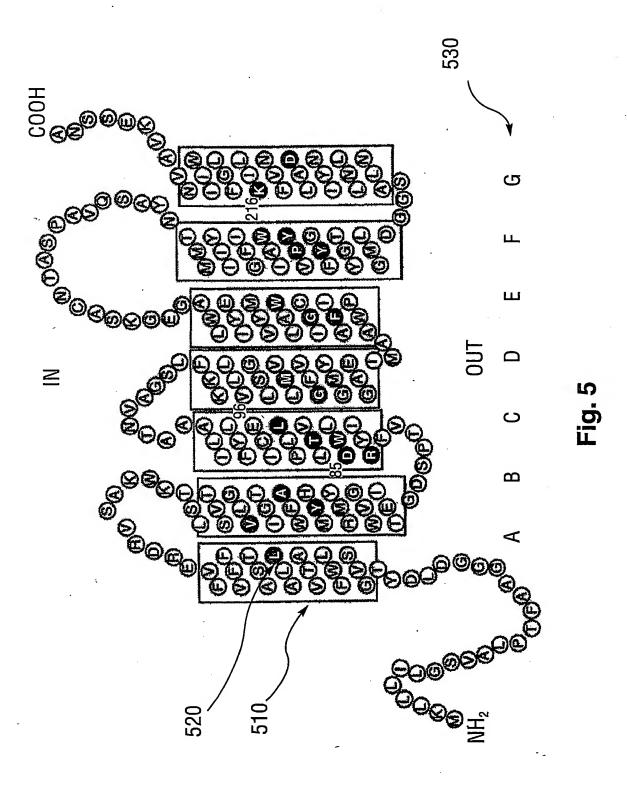
Figure

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384	432	480	228	576	624	672
tta Leu	gca Ala	tgg Trp 160	tgt Cys	tat Tyr	ggt Gly	tat Tyr
aaa t Lys I	gaa g Glu A	gct t Ala T	gca t Ala C 175	atg t Met T	aca g Thr G	atc t Ile T
aag Lys	ggt Gly	tta Leu	tot Ser	atg Met 190	ttc Phe	ctt Leu
ttt Phe 125	atg Met	tgt Cys	aaa Lys	aca Thr	tat Tyr 205	aac Asn
tta Leu	tac Tyr 140	ggg $_{ m G1Y}$	gga G1y	aac Asn	ggt Gly	tta Leu
tca Ser	ggt Gly	att 11e 155	gaa Glu	tac Tyr	gta Val	aac Asn
gga Gly	ttt Phe	att Ile	gga G1Y 170	gct Ala	cct Pro	ctt Leu
gct Ala	gtg Val	ttc Phe	gct Ala	tca Ser 185	tat Tyr	gct Ala
gtt Val 120	ctt Leu	gca Ala	tgg Trp	caa Gln	att Ile 200	tca Ser
aat Asn	atg Met 135	cct Pro	tta Leu	gtg Val	gcg Ala	gga G1 <u>y</u> 215
act Thr	gtt Val	tgg Trp 150	gaa Glu	gct Ala	tgg Trp	ggt Gly
gca Ala	ctt Leu	gca Ala	tat Tyr 165	cct Pro	ggt. Gly	gac Asp
gct Ala	tct Ser	gct Ala	att Ile	agt Ser 180	ttt Phe	ggt Gly
gct Ala 115	ggt Gly	atg Met	atg Met	gca Ala	atc Ile 195	atg Met
ctt Leu	gtt Val 130	atc Ile	tac Tyr	act Thr	atc Ile	ctg Leu
att Ile	cta Leu	gga G1 <u>y</u> 145	gta Val	aat Asn	att Ile	tac Tyr

Figure

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720	7.50
tgg Trp 240	
ata Ile	
att Ile	
tta Leu	
ggt Gly	
ttt Phe 235	
cta Leu	gct Ala 250
att Ile	aat Asn
aag Lys	tct Ser
aac Asn	tct Ser
gtt Val 230	gaa Glu
ttt Phe	aaa Lys 245
gac Asp	gtt Val
gct Ala	gct Ala
ctt Leu	gtt Val
aac Asn 225	aat Asn



48	96	144	192	240	. 58 8 8 8 7	336
aca Thr	gtt Val	ttc Phe	act Thr	atg Met 80	tac Tyr	ور تاریخ
						tta Leu
cct Pro 15	ggt Gly	ttt Phe	tta Leu	tac Tyr	aga Arg 95	tac Tyr
ctt. Leu	act Thr 30	gta Val	tca Ser	atg Met	ttt Phe	ttc Phe
gca Ala	tac Tyr	act Thr 45	aca Thr	tac Tyr	gta Val	gaa Glu
att Ile	gat Asp	tct Ser	aaa Lys 60	cat His	act Thr	tgt Cys
gtt Val	agt Ser	gca Ala	tgg Trp	tgg Trp 75	cca Pro	ata Ile
agt Ser 10	gct Ala	tta Leu	aaa Lys	ttc Phe	tcg Ser 90	ttg Leu
ggt Gly	gat Asp 25	cta Leu	gca Ala	gct Ala	gat Asp	cta Leu 105
tta Leu	ctt Leu	gct Ala 40	tct Ser	att Ile	ggt Gly	cct Pro
ata Ile	gac Asp	gct Ala	gtt Val 55	ggt Gly	act Thr	gtt Val
ctg Leu	ggt Gly	act Thr	aga Arg	act Thr 70	gag Glu	aca Thr
tta Leu 5	ggt Gly	gtt Val	gat Asp	gtt Val	att Ile 85	cta Leu
tta Leu	ggt Gly 20	tta Leu	aga Arg	ctt Leu	tgg Trp	tta Leu 100
aaa Lys	gca Ala	tgg Trp 35.	gaa Glu	ggt Gly	gta Val	tgg Trp
ggt Gly	gct Ala	ttt	gtt Val 50	tag Ser	ggg G $1_{ m Y}$	gat Asp
atg Met 1	ttt Phe	tct Ser	ttt Phe	gta Val 65	aga Arg	att Ile

Figure 6

384	432	480	528	576	624	672
aag aaa tta Lys Lys Leu	ggt gag gca Gly Glu Ala	tta gct tgg Leu Ala Trp 160	gct gca tgt Ala Ala C <u>y</u> s 175	atg atg tat Met Met Tyr 190	ttc aca ggt Phe Thr Gly	ctt atc tat Leu Ile Tyr
ctg ttt a Leu Phe I 125	tac atg g Tyr Met ( 140	ggg tgt t Gly Cys I	ggc aag g Gly Lys A	aac aca a Asn Thr M	ggt tat t Gly Tyr E 205	tta aac c Leu Asn I 220
ggc Gly	ggt Gly	att Ile 155	gaa Glu	tac Tyr	gta Val	aac Asn
gct gct Ala Ala	gtg ttt Val Phe	ttc gtt Phe Val	gct gga Ala Gly 170	tca gct Ser Ala 185	tat cct Tyr Pro	gct ctt Ala Leu
aat gtt Asn Val 120	atg ctt Met Leu 135	ggt gca Gly Ala	cta tgg Leu Trp	gtg caa Val Gln	gca att Ala Ile 200	gga tca Gly Ser 215
gca aca Ala Thr	ctt gtt Leu Val	gct tgg Ala Trp 150	tat gaa Tyr Glu 165	cct gct Pro Ala	ggt tgg Gly Trp	gac ggt Asp.Gly
gct gct Ala Ala 115	ggt tct Gly Ser	atg aac Met Asn A	att Hle	gca agt o Ala Ser 1 180	ttt Phe	ggt Gly
att ctt go Ile Leu A	ttg gtt gg Leu Val G	gga att at Gly Ile Me 145	gta tac atg Val Tyr Met	aat act go Asn Thr A]	ata atc atc Ile Ile Ile 195	tac cta atg Tyr Leu Met 210

Figure

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tgg Trp 240	
ata Ile	
att Ile	
tta Leu	
ggt Gly	
ttt Phe 235	
cta Leu	gct Ala 250
att Ile	aat Asn
aag Lys	tct Ser
aac Asn	tct Ser
gtt Val 230	gaa Glu
ttt Phe	aaa Lys 245
gac Asp	gtt Val
gct Ala	gct Ala
ctt Leu	gtt Val
gac Asp 225	aat Asn

48	96	144	192	240	288	336
aca Thr	gtt Val	ttc Phe	act Thr	atg Met 80	tac Tyr	tta Léu
cct Pro 15	ggt Gly	ttt Phe	tta Leu	tac Tyr	aga Arg 95	tac Tyr
ctt Leu	act Thr 30	gta Val	tca Ser	atg Met	ttt Phe	ttc Phe
gca Ala	tac Tyr	act Thr 45	aca Thr	tac Tyr	gta Val	gaa Glu
att Ile	gat Asp	tct Ser	aaa Lys 60	cat His	act Thr	tgt Cys
gtt Val	agt Ser	gca Ala	tgg Trp	tgg Trp 75	cca Pro	ata Ile
agt Ser 10	gct Ala	tta Leu	aaa Lys	ttc Phe	tcg Ser 90	tta Leu
ggt Gly	gat Asp 25	tta Leu	gca Ala	gct Ala	gat Asp	cta Leu 105
tta Leu	ctt Leu	gct Ala 40	tat Ser	att Ile	ggt Gly	cct Pro
ata Ile	gac Asp	gct Ala	gtt Val 55	ggt Gly	act Thr	gtt Val
ctg Leu	ggt Gly	act Thr	aga Arg	act Thr 70	gaa Glu	aca Thr
tta Leu 5	ggt Gly	gct Ala	gat Asp	gtt Val	att Ile 85	cta Leu
tta Leu	ggt Gly 20	tta Leu	aga Arg	ctt Leu	tgg Trp	tta Leu 100
ааа Lys	gca Ala	tgg Trp 35	gaa Glu	ggt Gly	gta Val	tgg Trp
ggt Gly	gct Ala	ttt Phe	gtt Val 50	tct Ser	ggg G $1\gamma$	gat Asp
atg Met 1	ttt Phe	tct Ser	ttt Phe	gta Val 65	aga Arg	att Ile

Figure

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384	432	480	528	576	624	672
tta Leu	gca Ala	tgg Trp 160	tgt Cys	tat Tyr	ggt Gly	tat Tyr
aaa Lys	gaa Glu	gct Ala	gca Ala 175	atg Met	aca Thr	atc Ile
aag Lys	ggt Gly	tta Leu	tct Ser	atg Met 190	ttc Phe	ctt
ttt Phe 125	atg Met	tgt Cys	aaa Lys	aca Thr	tat Tyr 205	aac Asn
tta Leu	tac Tyr 140	ggg G $1 \chi$	gga G1Y	aac Asn	ggt Gly	tta Leu 220
tca Ser	ggt Gly	att 11e 155	gaa Glu	tac Tyr	gta Val	aac Asn
gga Gly	ttt Phe	att Ile	gga Gly 170	gct Ala	cct Pro	ctt Leu
gct Ala	gtg Val	ttc Phe	gct Ala	tca Ser 185	tat Tyr	gct Ala
gtt Val 120	ctt Leu	gca Ala	tgg Trp	caa Gln	att Ile 200	tca Ser
aat Asn	atg Met 135	cct Pro	cta Leu	gtg Val	gcg Ala	gga G1Y 215
act Thr	gtt Val	tgg Trp 150	gaa Glu	gct Ala	tgg Trp	ggt Gly
gct Ala	ctt Leu	gca Ala	tat Tyr 165	cct Pro	ggt Gly	gac Asp
gct Ala	tct Ser	gct Ala	att Ile	agt Ser 180	ttt Phe	ggt Gly
gct Ala 115	ggt Gly	atg Met	atg Met	gca Ala	atc Ile 195	atg Met
ctt Leu	gtt Val 130	atc Ile	tac Tyr	act Thr	atc Ile	ctg Leu 210
att Ile	cta Leu	gga Gly 145	gta Val	aat Asn	att Ile	tac Tyr
						•

Figure .

720

tgg Trp 240

ata Ile

att Ile

tta Leu

ctt

aac Asn 225

aat gtt g Asn Val

ggt Gly						
ttt Phe 235				,		
cta Leu	gct Ala 250					
att Ile	aat Asn					
aag Lys	tct Ser					
aac Asn	tct Ser					
gtt Val 230	gaa Glu					
ttt Phe	aaa Lys 245		-			
gat Asp	gtt Val	•				,
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48	96	144	192	240	288	336
cct aca Pro Thr 15	ggt gtt Gly Val	ttt ttc Phe Phe	tta act Leu Thr	tac atg Tyr Met 80	aga tac Arg Tyr 95	tac tta Tyr Leu
ctt Leu	act Thr 30	gta t Val E	tca t Ser L	atg t Met T	ttt a Phe A 9	ttc t Phe T 110
gca Ala	tac Tyr	act Thr 45	aca Thr	tac Tyr	gta Val	gaa Glu
att Ile	gat Asp	tct Ser	aaa Lys 60	cat His	act Thr	tgt Cys
gtt Val	agt Ser	gca Ala	tgg Trp	tgg Trp 75	cct Pro	ata Ile
agt Ser 10	gct Ala	tta Leu	ааа Lys	ttc Phe	tcg Ser 90	tta Leu
ggt Gly	gat Asp 25	cta Leu	gca Ala	gct Ala	gat Asp	tta Leu 105
tta Leu	ctt Leu	gct Ala 40	tct Ser	att Ile	ggt Gly	cct Pro
ata Ile	gac Asp	gct Ala	gtt Val 55	ggt Gly	act Thr	gtt Val
ctg Leu	ggt Gly	aca Thr	aga Arg	act Thr 70	gaa Glu	aca Thr
tta Leu 5	ggc Gly	gtt Val	gat Asp	gtt Val	att Ile 85	cta Leu
tta Leu	ggt Gly 20	tta Leu	aga Arg	ctt Leu	tgg Trp	tta Leu 100
aaa Lys	gca Ala	tgg Trp 35	gaa Glu	ggt Gly	gta Val	tgg Trp
ggt Gly	gct Ala	ttt Phe	gtt Val 50	tct Ser	gga $_{ m G1Y}$	gat Asp
atg Met 1	ttt Phe	tct Ser	ttt Phe	gta Val 65	aga Arg	att Ile

384	432	<b>4</b> 80	22 8	576	624	672
		<b>-</b> 0 -	9			
ctt Leu	gca Ala	tgg Trp 160	tgt Cys	gct Ala	ggt Gly	tat Tyr
aaa Lys	gaa Glu	gct Ala	gca Ala 175	atg Met	aca Thr	att Ile
aag Lys	ggt $_{ m G1Y}$	tta Leu	tct Ser	atg Met 190	ttc Phe	ctt Leu
ttt Phe 125	atg Met	tgt Cys	ааа Lys	aca Thr	tat Tyr 205	aac Asn
tta Leu	tac Tyr 140	ggg G $1_Y$	gga Gly	aac Asn	ggt Gly	tta Leu 220
tca Ser	ggt Gly	att Ile 155	gaa Glu	tac Tyr	ata Ile	aac Asn
.ggc Gly	ttt Phe	att Ile	gga G1 <u>y</u> 170	gct Ala	cct Pro	ctt Leu
gcc Ala	gtg Val	ttc Phe	gct Ala	tca Ser 185	tat Tyr	gct Ala
gtt Val 120	ctt Leu	gca Ala	tat Tyr	caa G1n	att Ile 200	tca Ser
aat Asn	atg Met 135	cct Pro	cta Leu	gtt Val	gca Ala	gga G1y 215
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gca Ala	ctt Leu	gct Ala	tat Tyr 165	cct Pro	ggt Gly	gac Asp
gct Ala	tct Ser	gca Ala	att Hle	agt Ser 180	ttc Phe	ggt 31y
gct Ala 115	ggt Gly	atg Met	atg Met	gca Ala	gtc Val 195	atg g Met (
ctt Leu	gtt Val 130	att Ile	tac Tyr	act Thr	ata Ile	cta Leu 210
att Ile	cta . Leu	gga G1Y 145	gta Val	aat Asn	atc Ile	tac Tyr

Figure

720

tgg Trp 240	
ata Ile	
att Ile	
tta Leu	
ggt Gly	
ttt Phe 235	
cta Leu	gct Ala 250
att Ile	aat Asn
aag Lys	tct Ser
aac Asn	tct Ser
gtt Val 230	gaa Glu
ttt Phe	aaa Lys 245
gac Asp	gtt Val
gct Ala	gct Ala
ctt Leu	gtt Val
aac Asn 225	aat Asn

500	100 100 100 100	150 150 150 150	200 200 200 200	250 250 250 250	300 300 300 300
attaggTAGT GTTATTGCAC TTCCTACATT	TTGATGCTAG TGATTACACT GGTGTTTCTT	TTATTAGCAT CTACTGTATT TTTCTTTGTT C	AAAATGGAAA ACATCATTAA CTGTATCTGG	TCTGGCATTA CATGTACATG AGAGGGGTAT	CCAACTGTAT TTAGATACAT TGATTGGTTA
a tt	TTGA	TTAT C	аааа 	TCTG	CCAA
tattactgat	GGTGGTGACC	TACTGCTGCT	GAGTTTCTGC	GGTATTGCTT	TGGTGATTCG
atgggtaaat 	TGCTGCAGGT	TTTGGTTAGT	GAAAGAGATA	TCTTGTTACT	GGATTGAAAC
нннн	. 51 51 51 51	101 101 101 101	151 151 151 151	201 201 201 201	251 251 251 251
EBAC31A8 EBAC40 EBAC41 EBAC64	EBAC31A8 EBAC40 EBAC41 EBAC64	EBAC31A8 EBAC40 EBAC41 EBAC64	EBAC31A8 EBAC40 EBAC41 EBAC64	EBAC31A8 EBAC40 EBAC41 EBAC64	EBAC31A8 EBAC40 EBAC41 EBAC64

350 350 350 350	400 400 400 400	450 450 450 450	500 500 500 500	550 550 550 550	600 600 600 600
TTGCTGCTGC	GGTTCTCTTG	GGCTGCATGG .AACT	TTTATGAATTC.	CCTGCTGTGC	TTGGGCGATT
TACTTAATTC	ATTACTAGTTT.GC.T.	CAGGAATCAT	GTATACATGA	TACTGCAAGT	TCATCTTTGG
ATGTGAATTC	TATTTAAGAA .G	ATGGGTGAAG	TTTAGCTTGG	CTGCATGTAA	ATGTATATTA A.
CTCTATTAATG	GCTGGATCATCTGGCC	GTTTGGTTAC	TTATTGGGTG	GAAGGAAAAT CGG	CAACACAATG
CTAACAGTTC	AACTAATGTTA T	TTATGCTTGT	CCTGCATTCA GGG	ATGGGCTGGA	AATCAGCTTA
301 301 301 301	351 351 351 351	401 401 401 401	451 451 451 451	501 501 501 501	551 551 551 551
EBAC31A8 EBAC40 EBAC41 EBAC64	EBAC31A8 EBAC40 EBAC41 EBAC64	EBAC31A8 EBAC40 EBAC41 EBAC64	EBAC31A8 EBAC40 EBAC41 EBAC64	EBAC31A8 EBAC40 EBAC41 EBAC64	EBAC31A8 EBAC40 EBAC41 EBAC64

Figure

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SATCAGC 650	650	650	650	ָ כַּהַבָּוּ אָנֻ אַ אָנָאַ אָנָאַ		700	700	700	ttctaatgct 750	750	750	750	750	750	750	750	750	750
TATCCTGTAG GTTATTTCAC AGGTTACCTG ATGGGTGACG GTGGATCAGC			•		1 10111001	•	T		ttaaagaatc	•	•	•						
C AGGTTACCTG	Α	•	AA			g	• • • • • • • • • • • • • • • • • • • •		AATTATATGG AATGTTGCtg	•	•	•	•					
G GTTATTTCAC	•		•	היה מיידירי בע מי				E			•							
				1 かんがひるるのかひ			1		1 TATTTGGTTT									
EBAC31A8 601	EBAC40 601	EBAC41 601	EBAC64 601	1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1 1		EBAC40 651	EBAC41 651	EBAC64 651	EBAC31A8 70	EBAC40 70	EBAC41 70					EBAC41 701 EBAC64 701		

EBAC31A8	← ,	LGS	VIALPTFAAG	GGDLDASDYT	GVSFWLVTAA	LLASTVEFEV	20
40 <u>1</u>	<del>,                                    </del>	•	•	•		•	20
$41_{-1}$	Н	•	•	•	A	•	20
EBAC64_1	$\vdash$	•	•			•	20
EBAC31A8	51	KWK	TSLTVSGLVT	GIAFWHYMYM	RGVWTETGDS	PTVFRYTDWT.	100.
1 C Z Z K C L	, n						) ( ) (
T	٦ ·	•	•	•	•	•	7 O O
$\mathtt{EBAC41\_1}$	21	•	•	•	•	•	100
EBAC64_1	51	•	•	•		•	100
EBAC31A8	101	CEF	YLILAAATNV	AGSLFKKLLV	GSLVMLVFGY	MGEAGIMAAW	150
EBAC40 1	101	•	•	AG		N	150
$41^{-1}$	101	•	•	•	•		150
$\mathtt{EBAC64}^{-1}$	101	•	•	•	•	•	150
						3	
EBAC31A8	151	PAFIIGCLAW	CLAW VYMIYELWAG	EGKSACNTAS	PAVQSAYNTM	MYIIIFGWAI	200
40_1	151	GV	•	A	•	: •	200
EBAC41_1	151		•	•	•	•	200
64_1	151		. Y.	•	S	.AV	200
EBAC31A8	201	GYL	MGDGGSALNL	NLIYNLADEV	NKILFGLILW	NVAVKESSNA	250
EBAC40 1	201	•		D	•	•	250
41_1	201	•	•		•	•	250
64_1	201		•	•	•	•	250

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•				-		•
48	96	144	192	240	28 8	336
aca Thr	gtt Val	ttc Phe	act Thr	atg Met 80	tac Tyr	tta Leu
cct Pro 1	ggt g Gly 1	ttt t Phe E	tta a Leu 1	tac a Tyr M	aga t Arg 1 95	tac t Tyr I
ctt Leu	act Thr 30	gta Val	tca Ser	atg Met	ttt Phe	ttc Phe 110
gca Ala	tac Tyr	act Thr 45	aca Thr	tac Tyr	gta Val	gaa Glu
att Ile	gat	tct Ser	aaa Lýs 60	cat His	act Thr	tgt Cys
gtt: Val	agt	ı gca ı Ala	tgg Trp	ttc tgg Phe Trp 75	CCA	ata Ile
agt Ser 10	gct Ala	tta Leu	гааа Г <u>Г</u> УS		tcg Ser 90	. ttg . Leu
a ggt	gat 1 Asp 25	cta Leu	gca Ala	gct Ala	gat Asp	cta Leu 105
a tta e Leu	ctt Deu	gct A Ala 40	Ser	att Ile	ggt Gly	cct. Pro
g ata 1 Ile	rt gac Y Asp	t gct r Ala	a gtt g Val 55	ggt Gly	g acc 1 Thr	gtt : Val
a ctg u Leu	99	ac Th	ag Ar	act Thr 70	gag Glu	a aca 1 Thr
a tta u Leu 5	t ggt y Gly	a gtt u Val	a gat g Asp	t gtt u Val	g att o Ile 85	a cta ı Leu J
a tta s Leu	a ggt a Gly 20	g tta p Leu	a aga u Arg	t ctt Y Leu	a tgg 1 Trp	g tta o Leu 100
t aaa y Lys	t gca a Ala	t tgg e Trp 35	t gaa 1 Glu	g ggt r Gly	g gta Y Val	t tgg p Trp
g ggt t Gly	t gct 1e Ala	it ttt ir Phe	t gtt e Val 50	a tcg 1 Ser	a ggg g GlY	t gat e Asp
atg Met 1	ttt Phe	tot Ser	ttt Phe	gta Val	aga Arg	att Ile
				,		

Figure 11

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384	432	480	528	576	624	672
tta Leu	gca Ala	tgg Trp 160	tgt Cys	tat Tyr	ggt Gly	tat Tyr
aaa Lys	gag Glu	gct Ala	gca Ala 175	atg Met	aca Thr	atc Ile
aag Lys	ggt Gly	tta Leu	gct Ala	atg Met 190	ttc Phe	ctt Leu
ttt Phe 125	atg Met	tgt Cys	aag Lys	aca Thr	tat Tyr 205	aac Asn
ctg Leu	tac Tyr 140	ggg Gl $_{ m Y}$	ggc Gly	aac Asn	ggt Gly	tta Leu 220
${ m ggc}$	ggt Gly	att Ile 155	gaa Glu	tac Tyr	gta Val	aac Asn
gct Ala	ttt Phe	gtt Val	gga Gly 170	gct Ala	cct Pro	ctt Leu
gct Ala	gtg Val	ttc Phe	gct Ala	tca Ser 185	tat Tyr	gct Ala
gtt Val 120	ctt Leu	gca Ala	tgg Trp	caa Gln	att Ile 200	tca Ser
aat Asn	atg Met 135	ggt Gly	cta Leu	gtg Val	gca Ala	gga Gly 215
aca Thr	gtt Val	tgg Trp 150	gaa Glu	gct Ala	tgg Trp	ggt Gly
gca Ala	ctt Leu	gct Ala	tat Tyr 165	cct Pro	ggt Gly	gac Asp
gct Ala	tct Ser	aac Asn	att Ile	agt Ser 180	ttt Phe	ggt Gly
gct Ala 115	ggt Gly	atg Met	atg Met	gca Ala	atc Ile 195	atg Met
ctt Leu	gtt Val 130	att Ile	tac Tyr	act Thr	atc Ile	cta Leu 210
att Ile	ttg Leu	gga G1 <u>y</u> 145	gta Val	aat Asn	ata Ile	tac Tyr

Figure 11

720	750
att ata tgg Ile Ile Trp 240	
tta Leu	
ggt Gly	
ttt Phe 235	
cta Leu	gct Ala 250
att Ile	aat Asn
aag Lys	tct Ser
aac Asn	tat Ser
gtt Val 230	gaa Glu
ttt Phe	aaa Lys 245
gac Asp	gtt Val
gct Ala	gct Ala
ctt Leu	gtt Val
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96	144	192	240	288	336
tt gct gct ggt ggc gat cta gat ata agt gat act gtt ggt gtt ne Ala Ala Ala Gly Gly Asp Leu Asp Ile Ser Asp Thr Val Gly Val 25	the tigg ctg gtt aca gct ggt atg tta gcg gca act gtg ttc ttt br Phe Trp Leu Val Thr Ala Gly Met Leu Ala Ala Thr Val Phe 35	t gta gaa aga gac caa gtc agc gct aag tgg aaa act tca ctt gct he Val Glu Arg Asp Gln Val Ser Ala Lys Trp Lys Thr Ser Leu Ala 50	ta tot ggt tta att act ggt ata got ttt tgg cat tat oto tat atg il Ser Gly Leu Ile Thr Gly Ile Ala Phe Trp His Tyr Leu Tyr Met 75	ra ggt gtt tgg ata gac act ggt gat acc cca aca gta ttc aga tat g Gly Val Trp Ile Asp Thr Gly Asp Thr Pro Thr Val Phe Arg Tyr 90	att gat tgg tta tta act gtt cca tta caa atg gtt gag ttc tat cta Ile Asp Trp Leu Leu Thr Val Pro Leu Gln Met Val Glu Phe Tyr Leu 100
+- h-4	<b>₽</b> 01	TH CT	0 > 0	© < <b>₹</b>	αН·
	gct gct ggt ggc gat cta gat ata agt gat act gtt ggt gtt Ala Ala Gly Gly Asp Leu Asp Ile Ser Asp Thr Val Gly Val 20	gct gct gct ggt ggc gat cta gat ata agt gat act gtt ggt gtt Ala Ala Ala Gly Gly Asp Leu Asp Ile Ser Asp Thr Val Gly Val 25  ttc tgg ctg gtt aca gct ggt atg tta gcg gca act gtg ttc ttt Phe Trp Leu Val Thr Ala Gly Met Leu Ala Ala Thr Val Phe Phe 35	gct gct gct ggt ggc gat cta gat ata agt gat act gtt ggt gtt Ala Ala Ala Gly Gly Asp Leu Asp Ile Ser Asp Thr Val Gly Val 20  ttc tgg ctg gtt aca gct ggt atg tta gcg gca act gtg ttc ttt Phe Trp Leu Val Thr Ala Gly Met Leu Ala Ala Thr Val Phe Phe 35  gta gaa aga gac caa gtc agc gct aag tgg aaa act tca ctt gct Val Glu Arg Asp Gln Val Ser Ala Lys Trp Lys Thr Ser Leu Ala 55  school Ser Ala Lys Trp Lys Thr Ser Leu Ala Ala Ser Ala Lys Trp Lys Thr Ser Leu Ala	gct gct gct ggt ggc gat cta gat ata agt gat act gtt ggt gtt ha ha ha ha Gly Gly Asp Leu Asp Ile Ser Asp Thr Val Gly Val 25  ttc tgg ctg gtt aca gct ggt atg tta gcg gca act gtg ttc ttt Phe Trp Leu Val Thr Ala Gly Met Leu Ala Ala Thr Val Phe Phe 35  gta gaa aga gac caa gtc agc gct aag tgg aaa act tca ctt gct Val Glu Arg Asp Gln Val Ser Ala Lys Trp Lys Thr Ser Leu Ala 56  tct ggt tta att act ggt ata gct ttt tgg cat tat ctc tat atg Ser Gly Leu Ile Ala Phe Trp His Tyr Leu Tyr Met Ser Gly Leu Ile Thr Gly Ile Ala Phe Trp His Tyr Leu Tyr Met Ser Gly Leu Ile Thr Gly Ile Ala Phe Trp His Tyr Leu Tyr Met	t gct gct gct ggt ggc gat cta gat ata agt gat act gtt ggt gtt e Ala Ala Gly Gly Asp Leu Asp Ile Ser Asp Thr Val Gly Val 20 25 30 30 30 30 30 30 30 30 30 30 30 30 30

WO 01/83701	

384	432	480	528	576	624	672
g ctt s Leu	a gct ı Ala	a tgg 7 Trp 160	gta Val	atg Met	ggt a Gly	ata IIle
aag aag Lys Lys	ggc gaa Gly Glu	gct gga Ala Gly	gct gct Ala Ala 175	atg atg Met Met 190	gct gct Ala Ala	aac ctt Asn Leu
ttt Phe 125	gca Ala	atg Met	aag Lys	gca Ala	tat Tyr 205	tta Leu
tca tta Ser Leu	gga ttt Gly Phe 140	att ggt Ile Gly 155	gaa ggt Glu Gly	tac aac Tyr Asn	gct gga Ala Gly	ca aac er Asn 220
gct Ala	gct Ala	att Ile	ggt Gly 170	gca Ala	cct g Pro A	gct t Ala S
gtt gct Val Ala 120	tta ggt Leu Gly	gct ttc Ala Phe	tat atg Tyr Met	aac tct Asn Ser 185	att tat Ile Tyr 200	a tac 11 Tyr
agt g Ser Va	atg ti Met Le 135	cct go Pro A	cta ta Leu Ty	gtt aa Val As	gca at Ala Il 20	ggt gta Gly Val 215
t aca s Thr	a gta u Val	a tta 1 Leu 150	t gag r Glu 5	t gct o Ala	a tgg Y Trp	gaa Glu
gct tgt Ala Cys	tca tta Ser Leu	cct gta Pro Val	att tat Ile Tyr 165	agt cct Ser Pro 180	gtt gga Val Gly	ggt ggc Gly Gly
gct Ala 115	ggt Gly	gct Ala	atg Met	gca Ala	gtt Val 195	atg Met
att ctt Ile Leu	cta gct Leu Ala 130	gga tta Gly Leu 145	tta tac Leu Tyr	agt act Ser Thr	att att Ile Ile	tac cta Tyr Leu 210
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Figure 12

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atc att Ile Ile 240	,
tt Le	
ggt Gly	
ttt Phe	
cta Leu 235	gct Ala
att Ile	aat Asn 250
aag Lys	tct Ser
aac Asn	tct Ser
gtt Val	gaa Glu
ctt Leu 230	aaa Lys
gac Asp	gtt Val 245
gcc Ala	gct Ala
ctt Leu	gtt Val
aac Asn :	aat Asn
tat Tyr 225	tgg Trp

			27/108			
48	96	144	192	240	<b>5</b> 8 8 8 8 8 8 8 8 8 8 8 8 8 8 8 8 8 8 8	336
agt gct att gca ctt cca tca Ser Ala Ile Ala Leu Pro Ser 10	ata agt gat act gtt ggt gtt Ile Ser Asp Thr Val Gly Val 30	tta gcg gca act gta ttc ttt Leu Ala Ala Thr Val Phe Phe 45	aag tgg aaa act tca ctt act Lys Trp Lys Thr Ser Leu Thr 60	ttt tgg cat tat ctc tac atg Phe Trp His Tyr Leu Tyr Met 75	aca cca aca gta ttt aga tat Thr Pro Thr Val Phe Arg Tyr 90	caa atg gtt gag ttc tat cta Gln Met Val Glu Phe Tyr Leu 110
ctg ata tta ggt Leu Ile Leu Gly	ggc gat cta gat Gly Asp Leu Asp	aca gct ggt atg Thr Ala Gly Met 40	caa gtc agc gct Gln Val Ser Ala 55	act ggt ata gct Thr Gly Ile Ala 70	gat act ggt gat Asp Thr Gly Asp	act gtt cca tta Thr Val Pro Leu 105
atg ggt aaa tta tta Met Gly Lys Leu Leu 1 5	ttt gct gct gct ggt Phe Ala Ala Ala Gly 20	tca ttc tgg ctg gtt Ser Phe Trp Leu Val 35	ttt gta gaa aga gac Phe Val Glu Arg Asp 50	gta tct ggt tta att Val Ser Gly Leu Ile 65	aga ggt gtt tgg ata Arg Gly Val Trp Ile 85	att gat tgg tta tta Ile Asp Trp Leu Leu 100

Figure 13

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384	432	480	528	576	624	672
ctt Leu	gct Ala	tgg Trp 160	gta .val	aag Lys	ggt Gly	ata Ile
aag Lys	gaa Glu	gga Gly	gct Ala 175	atg : Met ]	gct Ala (	ctt den I
aag Lys	ggc Gly	gct Ala	gct Ala	atg a Met 1 190	gct Ala	aac d Asn 1
ttt Phe 125	gca Ala	atg Met	aag Lys	gca Ala l	tat Tyr 205	tta d Leu
tta Leu	ttt Phe 140	ggt Gly	ggt Gly	aac Asn	gga Gly	aac Asn 220
tca Ser	gga Gly	att Ile 155	gaa Glu	tac Tyr	gct	tca Ser
gct Ala	gct Ala	att Ile	ggt Gly 170	gca Ala	cct Pro	gct Ala
gct Ala	ggt Gly	ttc Phe	atg Met	tct Ser 185	tat Tyr	tac Tyr
gtt Val 120	tta Leu	gct Ala	cat His	aac Asn	att Ile 200	gta Val
agt Ser	atg Met 135	cct Pro	cta Leu	gtt Val	gca Ala	ggt Gly 215
aca Thr	gta Val	tta Leu 150	gag Glu	gct Ala	tgg Trp	gac Asp
tgt Cys	tta Leu	gta Val	tat Tyr 165	cct	gga $_{ m G1Y}$	ggt Gly
gct Ala	tca Ser	cct Pro	att Ile	agt Ser 180	att Ile	agt Ser
gct Ala 115	$\tt ggt\\ \tt Gly$	gct Ala	atg Met	gca Ala	gtt Val 195	atg Met
ctt Leu	gct Ala 130	tta Leu	tac Tyr	act Thr	att	cta Leu :210
att Ile	cta Leu	ggt Gly 145	tta Leu	agt Ser	att	tac Tyr
			•			

720

att Ile 240	
atc Ile	
ttg Leu	
ggt Gly	
ttt	
cta Leu 235	gct Ala
att Ile	aat Asn 250
aag Lys	tct Ser
aac Asn	tct Ser
gtt Val	gaa Glu
ttt Phe 230	aaa Lys
gac Asp	gtt Val 245
gct Ala	gct Ala
ctt Leu	gtt Val
aac Asn	aat Asn
tat Tyr 225	tgg Trp

tat Tyr 225

wo	Λ1	107	70	4
wi	111	//	/11	

gtt Val

ggt Gly

gtt Val 30

act Thr

gat Asp

agt Ser

ata Ile

cta Leu

gat Asp

ggc Gly

ggt Gly

gct Ala

gct Ala

gct Ala

ttt Phe

20

gat Asp 25

144

ttt Phe

ttc Phe

gtg Val

gca Ala

gcg Ala

tta Leu

atg Met

gct Ala

aca Thr

gtt Val

ctg Leu

tgg

ttc Phe

tca Ser

Trp 35

ggt Gly 40

act Thr 45

48

tca Ser

cca

ctt Leu

Ala gca

Ile att

gct Ala

agt Ser

ggt Gly

Ile

Leu Leu 5

Leu tta

Lys

Met 1

tta Leu

ata

ctg

tta

aaa

ggt Gly

atg

10

Pro 15

n/	

192

act Thr

tca Ser

act Thr

tgg Trp

aag Lys

gct Ala

agc Ser

gtc Val

caa Gln

gac Asp

aga Arg

gaa Glu

Val

50

gta

ttt Phe

55

aaa Lys09

Leu

ctt

tta

ggt

tct

Len

 $_{
m G1y}$ 

Ser

gta Val

Trp

tgg

gtt Val

ggt G1y

aga Arg

Leu 100

tta

tgg Trp

gat Asp

att Ile

	•	PCT/US01/14394
240	288	336
N	(4)	<b>.</b>
atg Met 80	tat Tyr	cta Leu
tat Tyr	aga Arg 95	tat Tyr
ctc Leu	ttc Phe	ttc Phe 110
tat Tyr	gta ttc Val Phe	gag Glu
cat His	aca Thr	gtt Val
tgg Trp 75	cca Pro	gtg Val
ttt Phe	acc Thr 90	caa Gln
gct Ala	gat Asp	tta Leu 105
ata Ile	ggt gat Gly Asp	cca Pro
ggt Gly	act Thr	gtt Val
act Thr 70	gac Asp	act Thr
att Ile	ata Ile 85	tta Leu

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384	432	480	528	576	624	672
ctt Leu	gct Ala	tgg Trp 160	gta Val	atg Met	ggt Gly	ata Ile
aag Lys	gaa Glu	gga t Gly I	gct g Ala V 175	atg a Met M	gct g Ala G	ctt a Leu I
aag Lys	ggc Gly	gct Ala	gct Ala	atg Met 190	gct Ala	aac Asn
ttt Phe 125	gca Ala	atg Met	aag Lys	gca Ala	tat Tyr 205	tta Leu
tta Leu	ttt Phe 140	ggt Gly	ggt Gly	aac Asn	gga Gly	aac Asn 220
tca Ser	gga G1y	att I1e 155	gaa Glu	tac Tyr	gct Ala	tca Ser
gct Ala	gct Ala	att Ile	ggt Gly 170	gca Ala	cct Pro	gct Ala
gct Ala	ggt Gly	ttc Phe	atg. Met	tct Ser 185	tat Tyr	tac Tyr
gtt Val 120	tta Leu	gct Ala	tat Tyr	aac Asn	att Ile 200	gta Val
agt Ser	atg Met 135	cct Pro	cta Leu	gtt Val	gca Ala	ggt Gly 215
aca Thr	gta Val	tta Leu 150	gag Glu	gct Ala	tgg Trp	gaa Glu
tgt Cys	tta Leu	gta Val	tat Tyr 165	cct Pro	gga Gly	ggc Gly
gct Ala	tca Ser	cct Pro	att Ile	agt Ser 180	gtt Val	ggt Gly
gct Ala 115	ggt Gly	gct Ala	atg Met	gca Ala	gtt Val 195	atg Met
ctt Leu	gct Ala 130	tta Leu	tac Tyr	act Thr	att Ile	cta Leu 210
att Ile	cta Leu	gga G1y 145	tta Leu	agt Ser	att Ile	tac Tyr

720	753
ttt ggt ttg atc att Phe Gly Leu Ile Ile 240	
cta Leu 235	gct Ala
att Ile	aat Asn 250
aag Lys	tct Ser
aac Asn	tct Ser
gtt Val	gaa Glu
ttt Phe 230	aaa Lys
gac Asp	gtt Val 245
gct Ala	gct Ala
ctt Leu	gtt Val
aac Asn	aat Asn
tat Tyr 225	tgg Trp

•						
48	9	144	192	240	. 888	336
cca tca Pro Ser 15	ggt gtt Gly Val	ttc ttt Phe Phe	ctt act Leu Thr	tat atg Tyr Met 80	aga tat Arg Tyr 95	tat cta Tyr Leu
ctt Leu	gtt Val 30	gtg Val	tca Ser	ctc Leu	ttc Phe	ttc Phe 110
att gca Ile Ala	gat act Asp Thr	gca act Ala Thr 45	aaa act Lys Thr 60	cat tat His Tyr	aca gta Thr Val	gtt gag Val Glu
agt gct Ser Ala 10	ata agt Ile Ser	tta gcg Leu Ala	aag tgg Lys Trp	ttt tgg Phe Trp 75	acc cca Thr Pro 90	caa atg Gln Met
ggt Gly	gat Asp 25	atg Met	gct Ala	gct Ala	gat Asp	tta Leu 105
ata tta Ile Leu	gat cta Asp Leu	gct ggt Ala Gly 40	gtc agc Val Ser 55	ggt ata Gly Ile	act ggt Thr Gly	gtt cca Val Pro
tta ctg Leu Leu 5	ggt ggc Gly Gly	gtt aca Val Thr	gac caa Asp Gln	att act Ile Thr 70	ata gac Ile Asp 85	act Thr
tta Leu	gct Ala 20	ctg Leu	aga Arg	tta Leu	tgg Trp	tta tta Leu Leu 100
ggt aaa Gly Lys	gct gct Ala Ala	ttc tgg Phe Trp 35	gta gaa Val Glu 50	tct ggt Ser Gly	ggt gtt Gly Val	gat tgg Asp Trp
atg Met (	ttt Phe 1	tca t Ser ]	ttt g Phe 1	gta t Val 9 65	aga g Arg (	att g Ile A

Figure 15

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384	432	480	528	576	624	672
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ctt Leu	gct Ala	tgg Trp 160	gta Val	gtg Val	ggt Gly	ata Ile
aag Lys	gaa Glu	gga Gly	gct Ala 175	atg Met	gct Ala	ctt Leu
aag Lys	ggc $_{ m G1Y}$	gct Ala	gct Ala	atg Met 190	gct Ala	aac Asn
ttt Phe 125	gca Ala	atg Met	aag Lys	gca Ala	tat Tyr 205	tta Leu
tta Leu	ttt Phe 140	ggt Gly	ggt Gly	aac Asn	gga Gly	aac Asn 220
tca Ser	gga Gly	att 11e 155	gaa G1u	tac Tyr	gct Ala	tca Ser
gct Ala	gct Ala	att Ile	ggt Gly 170	gca Ala	cct Pro	gct Ala
gct Ala	ggt Gly	ttc Phe	atg Met	tct Ser 185	tat Tyr	tac Tyr
gtt Val 120	tta Leu	gct Ala	tat Tyr	aac Asn	att Ile 200	gta Val
aat Asn	atg Met 135	cct Pro	cta Leu	gtt Val	gca Ala	ggt Gly 215
aca Thr	gta Val	tgg Trp 150	gag Glu	gct Ala	tgg Trp	gaa Glu
tgt Cys	tta Leu	gta Val	tat Tyr 165	cct	gga Gly	ggc Gly
gct Ala	tca Ser	cct	att Ile	agt Ser 180	gtt Val	ggt Gly
gct Ala 115	ggt Gly	gct	atg Met	gca Ala	gtt Val 195	atg Met
ctt Leu	gct Ala 130	ttg Leu	tac Tyr	act Thr	att Ile	cta Leu 210
att Ile	cta Leu	gga G1 <u>y</u> 145	tta Leu	agt Ser	att Ile	tac Tyr
			•			

Figure 15

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att Ile 240	
atc Ile	
ttg Leu	
ggt Gly	
ttt Phe	
cta Leu 235	gct Ala
att Ile	aat Asn 250
aag Lys	tct Ser
aac Asn	tct Ser
gtt Val	gaa Glu
ctt Leu 230	aaa Lys
gac Asp	gtt Val 245
gcc Ala	gct Ala
ctt Leu	gtt Val
aac Asn	aat Asn
tat Tyr 225	tgg Trp

D	CT/	TIC	Λ1	11 4	394
_ r	-11	UG	WI/	14	374

WO 01/83701	36/108	PCT/US01/14394
	30/100	

48	96	. 144	192	240	288	336
aca Thr	gtt Val	ttc Phe	act Thr	atg Met 80	tac Tyr	tta Leu
cct Pro 15	ggt Gly	ttt Phe	tta Leu	tac Tyr	aga Arg 95	tac Tyr
ctt Leu	act Thr 30	gta Val	tca Ser	atg Met	ttt Phe	ttc Phe 110
gca Ala	tac Tyr	act Thr 45	aca Thr	tac Tyr	gta Val	gaa Glu
att Ile	gat Asp	tct Ser	aaa Lys 60	cat His	act Thr	tgt Cys
gtt Val	agt Ser	gca Ala	tgg Trp	tgg Trp 75	cca Pro	ata Ile
agt Ser 10	gct Ala	tta Leu	aaa Lys	ttc Phe	tcg Ser 90	ttg Leu
ggt Gly	gat Asp 25	cta Leu	gca Ala	gct Ala	gat Asp	cta Leu 105
tta Leu	ctt Leu	gct Ala 40	tct Ser	att Ile	$\texttt{ggt}\\ \texttt{Gl}_{Y}$	cct Pro
ata Ile	gac Asp	gct Ala	gtt Val 55	ggt Gly	act Thr	gtt Val
ctg Leu	ggt Gly	act Thr	aga Arg	act Thr 70	gag Glu	aca Thr
tta Leu 5	ggt Gly	gtt Val	gat Asp	gtt Val	att Ile 85	cta Leu
tta Leu	ggt Gly 20	tta Leu	aga Arg	ctt Leu	tgg Trp	tta Leu 100
aaa Lys	gca Ala	tgg Trp 35	gaa Glu	ggt Gly	gta Val	tgg Trp
ggt Gly	gct Ala	ttt Phe	gtt Val 50	tct Ser	ggg G $1_{ m Y}$	gat Asp
atg Met 1	ttt Phe	tct Ser	ttt Phe	gta Val 65	aga Arg	att 11e

Figure 16

P	CT	Λī	Sn	1/	1 /	30	4
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WO 01/83701		. 4	PCT/US01/14394
	37/108		

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384	432	480	528	576	624	672
tta Leu	gca Ala	tgg Trp 160	tgt Cys	gct Ala	ggt Gly	tat Tyr
aaa Lys	gag Glu	gct Ala	gca t Ala ( 175	atg Met	aca Thr	att Ile
aag Lys	ggt Gly	tta Leu	tct Ser	atg Met 190	ttc Phe	ctt Leu
ttt Phe 125	atg Met	tgt Cys	aaa Lys	aca Thr	tat Tyr 205	aac Asn
ctg .Leu	tac Tyr 140	ggg G $1_{Y}$	gga $_{ m G1Y}$	aac Asn	ggt Gly	tta Leu 220
ggc Gly	ggt Gly	att 11e 155	gaa Glu	tac Tyr	gta Val	aac Asn
gct Ala	ttt Phe	att Ile	gga Gly 170	gct Ala	cct	ctt Leu
gct Ala	gtg Val	ttc Phe	gct Ala	tca Ser 185	tat Tyr	gct Ala
gtt Val 120	ctt Leu	gca Ala	tat Tyr	caa Gln	att Ile 200	tca Ser
aat Asn	atg Met 135	cct Pro	cta Leu	gtt Val	gca Ala	gga G1y 215
aca Thr	gtt Val	tgg Trp 150	gaa Glu	tcg Ser	tgg Trp	ggt Gly
gca Ala	ctt Leu	gct Ala	tat Tyr 165	cct	ggt Gly	gac Asp
gct Ala	tct Ser	aac Asn	att Ile	agt Ser 180	ttc Phe	ggt Gly
gct Ala 115	ggt Gly	atg Met	atg Met	gca Ala	gtc Val 195	atg Met
ctt Leu	gtt Val 130	att Ile	tac Tyr	act Thr	ata Ile	cta Leu 210
att Ile	ttg Leu	gga G1 <u>Y</u> 145	gta Val	aat Asn	atc Ile	tac TYr

7	)
Figure	

720	750
tta att ata tgg Leu Ile Ile Trp 240	
ggt t Gly I	
ttt Phe 235	
cta Leu	gct Ala 250
att Ile	aat Asn
aag Lys	tct Ser
aac Asn	tct Ser
gtt Val 230	gaa Glu
ttt Phe	aaa Lys 245
gac Asp	gtt Val
gct Ala	gct Ala
ctt	gtt Val
aac Asn 225	aat Asn

48	96 ,	144	192	240	288	336
t aca o Thr	rt gtt Y Val	t ttc le Phe	a act u Thr	c atg r Met 80	a tac g Tyr	c tta r Leu
ctt cct Leu Pro 15	act ggt Thr Gly 30	gta ttt Val Phe	tca tta Ser Leu	atg tac Met Tyr	ttt aga Phe Arg 95	ttc tac Phe Tyr 110
t gca e Ala	t tac o Tyr	r act r Thr 45	a aca s Thr	tac s Tyr	gta r Val	gaa Glu
gtt att Val Ile	agt gat Ser Asp	gca tct Ala Ser	tgg aaa Trp Lys 60	tgg cat Trp His 75	cca act Pro Thr	ata tgt Ile Cys
agt g Ser V 10	gct a Ala S	tta g Leu A	aaa t Lys T	ttc t Phe T	tcg c Ser P 90	tta a Leu I
a ggt 1 Gly	t gat 1 Asp 25	tta a Leu	gca Ala	gct Ala	gat Asp	cta Leu 105
ata tta Ile Leu	gac ctt Asp Leu	gct gct Ala Ala 40	gtt tct Val Ser 55	ggt att Gly Ile	act ggt Thr Gly	gtt cct Val Pro
ctg a Leu I	ggt g Gly A	act g Thr A	aga g Arg Va	act gr Thr G 70	gaa a Glu T	aca g Thr V
a tta u Leu 5	t ggt Y Gly	a gtt u Val	a gat g Asp	t gtt 1 Val	g att o Ile 85	a cta 1 Leu )
aaa tta Lys Leu	gca ggt Ala Gly 20	tgg tta Trp Leu 35	gaa aga Glu Arg	ggt ctt Gly Leu	gta tgg Val Trp	tgg tta Trp Leu 100
ggt a Gly L	gct g Ala A	ttt to Phe T: 33	gtt ga Val G	tct g Ser G	ggg g <sup>†</sup> Gly Va	gat tç Asp Tı
atg Met 1	ttt Phe	tct Ser	ttt Phe	gta Val 65	aga Arg	att Ile

Figure 1

384	432	480	528	576	624	672
tta Leu	gca Ala	tgg Trp 160	tgt Cys	atg Met	ggt Gly	tat Tyr
ааа Lys	gaa Glu	gct Ala	gcg Ala 175	atg Met	aca Thr	atc Ile
aag Lys	ggt Gly	tta Leu	gct Ala	atg Met 190	ttc Phe	ctt Leu
ttť Phe 125	atg Met	tgt Cys	aaa Lys	aca Thr	tat Tyr 205	aac Asn
ctg Leu	tac Tyr 140	ggg Gl $y$	gga Gly	aac Asn	ggt Gly	tta Leu 220
ggc Gly	ggt Gly	att Ile 155	gaa Glu	tac Tyr	gta Val	aac Asn
gct Ala	ttt Phe	gtt Val	gga G1y 170	gct Ala	cct Pro	ctt Leu
gct Ala	gtg Val	ttc Phe	ctt Leu	tca Ser 185	tat Tyr	gca Ala
gtt Val 120	ctt Leu	gca Ala	tgg Trp	cag Gln	att Ile 200	tca Ser
aat Asn	atg Met 135	ggt Gly	ctt Leu	gtt Val	gca Ala	gga G1y 215
act Thr	gtt Val	tgg Trp 150	gag Glu	gct Ala	tgg Trp	ggt Gly
gct Ala	ctt Leu	gct Ala	tat Tyr 165	cct Pro	ggt Gly	gac Asp
gct Ala	tct Ser	aac Asn	att Ile	agt Ser 180	ttt Phe	ggt Gly
gct Ala 115	ggt Gly	atg Met	atg Met	gca Ala	atc Ile 195	atg Met '
ctt Leu	gtt Val 130	att Ile	tac Tyr	aca Thr	atc Ile	cta Leu 210
att Ile	ttg Leu	gga G1y 145	gta Val	aat Asn	atc Ile	tac Tyr

Figure 1

7			
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tgg Trp 240

ata Ile

att Ile

tta Leu

ggt Gly

ttt Phe 235

cta Leu

att Ile

aag Lys

aac Asn

ttt Phe

gac Asp

gct

aac Asn 225

ctt Leu

gtt Val 230

gct Ala 250 aat Asn

tct Ser

tct Ser

gaa Glu

gtt Val

gct Ala

gtt Val

aat Asn

aaa Lys 245

41/108

PCT/US01/14394

WO 01/83701		42/108	PCT/US01/14394

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48	96	144	192	240	28 8 7	336
t aca o Thr	t gtt 7 Val	ttc Phe	a act 1 Thr	atg Met 80	rtac Tyr	tta
ctt cct Leu Pro 15	act ggt Thr Gly 30	gta ttt Val Phe	tca tta Ser Leu	atg tac Met Tyr	ttt aga Phe Arg 95	ttc tac Phe Tyr 110
gca c Ala L	tac a Tyr TJ 3(	act gi Thr Ve 45	aca to Thr Se	tac at Tyr Me	gta tt Val Pł	gaa tt Glu Ph
t att 1 Ile	c gat r Asp	tct Ser	aaa Lys 60	cat His	act Thr	tgt Cys
agt gtt Ser Val 10	gct agt Ala Ser	tta gca Leu Ala	aaa tgg Lys Trp	ttc tgg Phe Trp 75	tog cca Ser Pro 90	tta ata Leu Ile
ggt a Gly s 1	gat g Asp A 25	tta t Leu L	gca aa Ala Ly	gct ti Ala Pl	gat to Asp Se	cta tt Leu Le 105
a tta	ctt Leu	gct Ala 40	Ser	att Ile	ggt Gly	cct Pro
ctg ata Leu Ile	ggt gac Gly Asp	act gct Thr Ala	ga gtt ig Val 55	ct ggt hr Gly 0	ia act .u Thr	a gtt r Val
tta ci Leu Le 5	ggt gg Gly G	gtt ac Val Th	gat aga Asp Arg	gtt act Val Thr 70	att gaa Ile Glu 85	cta aca Leu Thr
tta Leu	ggt Gly 20	tta Leu	aga Arg	ctt Leu	tgg Trp	tta Leu 100
jt aaa Y Lys	t gca .a Ala	t tgg le Trp 35	t gaa 1 Glu	t ggt r Gly	g gta y Val	t tgg p Trp
atg ggt Met Gly 1	ttt gct Phe Ala	tct ttt Ser Phe	ttt gtt Phe Val 50	gta tct Val Ser 65	aga ggg Arg Gly	att gat Ile Asp

<b>WO</b> 01/83701		PCT/US01/14394
	43/108	

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384	432	480	528	576	624	672
tta Leu	gca Ala	tgg Trp 160	tgt Cys	tat Tyr	ggt Gly	tat Tyr
aaa Lys	gag Glu	gct Ala	gca Ala 175	atg Met	aca Thr	atc Ile
aag Lys	ggt Gly	tta Leu	gct Ala	atg Met 190	ttc Phe	ctt Leu
ttt Phe 125	atg Met	tgt Cys	aag Lys	aca Thr	tat Tyr 205	aac Asn
ctg Leu	tac Tyr 140	ggg G $1Y$	ggc	aac Asn	ggt Gly	tta Leu 220
ggc $_{ m GLY}$	ggt Gly	att Ile 155	gaa Glu	tac Tyr	gta Val	aac Asn
gct Ala	ttt Phe	gtt Val	gga Gly 170	gct Ala	cct Pro	ctt Leu
gct Ala	gtg Val	ttc Phe	gct Ala	tca Ser 185	tat Tyr	gct Ala
gtt Val 120	ctt Leu	gca Ala	tgg Trp	caa Gln	att Ile 200	tca Ser
aat Asn	atg Met 135	ggt Gly	cta Leu	gtg Val	gca Ala	gga Gly 215
act Thr	gtt Val	tgg Trp 150	gaa Glu	gct Ala	tgg Trp	ggt Gly
gca Ala	ctt	gct Ala	tat Tyr 165	cct Pro	ggt Gly	gac Asp
gct Ala	ser	aac Asn	att Ile	agt Ser 180	ttt Phe	ggt Gly
gct Ala 115	ggt Gly	atg Met	atg Met	gca Ala	atc Ile 195	atg Met
ctt Leu	gtt Val 130	att Ile	tac Tyr	act Thr	atc Ile	cta Leu 210
att	ttg Leu	gga Gly 145	gta Val	aat Asn	ata Ile	tac Tyr

720	750
ggt tta att ata tgg Gly Leu Ile Ile Trp 240	
ttt Phe 235	
cta Leu	gct Ala 250
att Ile	aat Asn
aag Lys	tct Ser
aac Asn	tct Ser
gtt Val 230	gaa Glu
ttt Phe	aaa Lys 245
gac Asp	gtt Val
gct Ala	gct Ala
ctt Leu	gtt Val
aac Asn 225	aat Asn

48	96	144	192	240	288	336
ø Н	т н	ບ ພຸ	ц ц	t g	В	В Д
aca Thr	gtt. Val	ttc	act Thr	atg Met 80	tac Tyr	tta Leu
cct Pro 15	ggt Gly	ttt Phe	tta Leu	tac Tyr	aga Arg 95	tac Tyr
ctt Leu	act Thr 30	gta Val	tca Ser	atg Met	ttt Phe	ttc Phe 110
gca Ala	tac Tyr	act Thr 45	aca Thr	tac Tyr	gta Val	gaa Glu
att Ile	gat Asp	tat Ser	aaa Lys 60	cat His	act Thr	tgt Cys
gtt Val	agt Ser	gca Ala	tgg Trp	tgg Trp 75	cca Pro	ata Ile
agt Ser 10	gct Ala	tta Leu	aaa Lys	ttc Phe	tcg Ser 90	tta Leu
ggt Gly	gat Asp 25	cta Leu	gca Ala	gct Ala	gat Asp	cta Leu 105
ťta Leu	ctt Leu	gct Ala 40	tct Ser	att Ile	${ t ggt}$	cct Pro
ata Ile	gac Asp	gct Ala	gtt Val 55	ggt Gly	act Thr	gtt Val
ctg Leu	ggt Gly	aca Thr	aga Arg	act Thr 70	gaa Glu	aca Thr
tta Leu 5	ggc Gly	gtt Val	gat Asp	gtt Val	att Ile 85	cta Leu
tta Leu	ggt Gly 20	tta Leu	aga Arg	ctt Leu	tgg Trp	tta Leu 100
aaa Lys	gca Ala	tgg Trp 35	gaa Glu	ggt Gly	gta Val	tgg Trp
ggt GlY	gct Ala	ttt Phe	gtt Val 50	tct Ser	$^{\tt ggg}_{\tt G1y}$	gat Asp
atg Met 1	ttt Phe	tct Ser	ttt Phe	gta Val 65	aga Arg	att Ile

Figure 19

					• .	
384	432	480	22 8	576	624	672
tta Leu	gca Ala	tgg Trp 160	tgt Cys	n L A	ggt Gly	tat Tyr
aaa t Lys L	gaa g Glu A	gct t Ala II	gca t Ala C 175	atg gc Met Al	aca g Thr G	att t ïle T
aag a Lys I	ggt g Gly G	tta g Leu A	ser 7	atg a Met M	ttc a Phe I	ctt a Leu I
ttt Phe 125	atg Met	tgt Cys	aaa Lys	aca Thr	tat Tyr 205	aac Asn
tta Leu	tac Tyr 140	ggg Gl $_{ m Y}$	gga $_{ m G1Y}$	aac Asn	ggt Gly	tta Leu 220
tca Ser	ggt Gly	att Ile 155	gaa Glu	tac Tyr	gta Val	aac Asn
gga Gly	r ttt. . Phe	att Ile	. gga . Gly 170	gct Ala	cct Pro	ctt
gct Ala	gtg Val	t ttc Phe	gct Ala	tca Ser 185	tat Tyr	gct Ala
gtt Val 120	ctt Leu	gca Ala	t tat I Tyr	caa Gln	att Ile 200	tca Ser
aat Asn	t atg 1 Met 135	g cct	ı cta ı Leu	gtt : Val	gca Ala	ggg Gly 215
t act a Thr	gt Va	a tgg a Trp 150	c gaa c Glu	tcg Ser	tgg Trp	s ggt 9 Gly
t gct a Ala	t ctt r Leu	t gca a Ala	t tat e Tyr 165	t cct r Pro 0	c ggt e Gly	t gac Y Asp
t gct a Ala 5	gt tct 1y Ser	g gct t Ala	g att t Ile	a agt a Ser 180	c ttc 1 Phe 5	g ggt t Gly
t gct su Ala 115	തയ	tt atg le Met	ıc atg r Met	it gca Ir Ala	a gtc e Val 195	a atg u Met .0
att ctt Ile Leu	cta gtt Leu Val 130	aa at In Il 45	tacal Tyr	aat act Asn Thr	atc ata Ile Ile	tac cta Tyr Leu 210
g H	μΩ	8 6 7	gta Val	a As	g H	Ţ Ţ

Figure 19

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b	)
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720	750
tgg Trp 240	
ata Ile	
att Ile	
tta Leu	
ggt Gly	
ctt Leu 235	
cta Leu	gct Ala 250
att Ile	aat Asn
aag Lys	tct Ser
aac Asn	ser.
gtt Val 230	gaa Glu
ttt Phe	aaa Lys 245
gac Asp	gtt Val
gct Ala	gct Ala
ctt Leu	gtt Val
aac Asn 225	aat Asn

48	96	144	192	240	288	336
aca Thr	gtt Val	ttc Phe	act Thr	atg Met 80	tac Tyr	tta Leu
cct Pro 15	ggt Gly	ttt Phe	tta Leu	tac Tyr	aga Arg 95	tac Tyr
ctt Leu	act Thr 30	gta Val	tca Ser	atg Met	ttt Phe	ttc Phe 110
gca Ala	tac Tyr	act Thr 45	aca Thr	tac Tyr	gta Val	gaa Glu
att Ile	gat Asp	Ser	aaa Lys 60	cat	act Thr	tgt Cys
gtt Val	agt Ser	gca Ala	tgg Trp	tgg Trp 75	cca Pro	ata Ile
agt Ser 10	gct Ala	tta Leu	aaa Lys	ttc Phe	tag Ser 90	tta Leu
ggt Gly	gat Asp 25	tta Leu	gca Ala	gct Ala	gat Asp	cta Leu 105
tta Leu	ctt Leu	gct Ala 40	tct Ser	att Ile	ggt Gly	cct Pro
ata Ile	gac Asp	gct Ala	gtt Val 55	ggt Gly	act Thr	gtt Val
ctg Leu	ggt Gly	act Thr	aga Arg	act Thr 70	gaa Glu	aca Thr
tta Leu 5	ggt Gly	gtt Val	gat	gtt Val	att Ile 85	cta Leu
tta Leu	ggt Gly 20	tta Leu	aga Arg	ctt Leu	tgg Trp	tta Leu 100
aaa Lys	gca Ala	tgg Trp 35	gaa Glu	ggt Gly	gta Val	tgg Trp
ggt Gly	gct Ala	ttt Phe	gtt Val 50	tct Ser	ggg Gl $_{Y}$	gat Asp
atg Met 1	ttt Phe	tct Ser	ttt	gta Val 65	aga Arg	att

Figure 20

			43/10			
384	432	480	528	576	624	672
gct aat gtt gct gga tca tta ttt aag aaa tta Ala Asn Val Ala Gly Ser Leu Phe Lys Lys Leu 120	gtt atg ctt gtg ttt ggt tac atg ggt gaa gca Val Met Leu Val Phe Gly Tyr Met Gly Glu Ala 135	tgg cct gca ttc att att ggg tgt tta gct tgg Trp Pro Ala Phe Ile Ile Gly Cys Leu Ala Trp 150	gaa tta tgg gct gga gaa gga aaa tct gca tgt Glu Leu Trp Ala Gly Glu Gly Lys Ser Ala Cys 170	gct gtg caa tca gcc tac aac aca atg atg tat Ala Val Gln Ser Ala Tyr Asn Thr Met Met Tyr 185	tgg gcg att tat cct gta ggt tat ttc aca ggt Trp Ala Ile Tyr Pro Val Gly Tyr Phe Thr Gly 200	ggt gga tca gct ctt aac tta aac ctt atc tat Gly Gly Ser Ala Leu Asn Leu Asn Leu Ile Tyr 215
rct gct gca la Ala Ala 15	gt tct ctt 1y Ser Leu	tg gct gca et Ala Ala	att ta Ile Ty 16	ca agt cct la Ser Pro 180	tc ttt ggt le Phe Gly 95	tg ggt gac et Gly Asp
gtt gct Val Ala 120	ctt gtg Leu Val	gca ttc Ala Phe	gct Ala	tca Ser 185	tat Tyr	tca gct Ser Ala
att ctt gct g Ile Leu Ala A 115	cta gtt ggt to Leu Val Gly So 130	ga atc atg ly Ile Met 45	gta tac atg a Val Tyr Met I	at act gca sn Thr Ala	tt atc atc le Ile Ile 195	tac ttg atg gg Tyr Leu Met G 210
	<b>У</b> Н	ያ ቤ ኅ	OI 12	Q K	Ø H	T F

Figure 20

720

ata tgg Ile Trp 240		. *		
att Ile				
tta Leu				
ggt Gly				
ttt Phe 235				
cta Leu	gct Ala 250			
att Ile	aat Asn			
aag Lys	tct Ser			
aac Asn	tct Ser			
gtt aac Val·Asn 230	gaa Glu			
ttt Phe	aaa Lys 245			
gac Asp	gtt Val			
gct Ala	gct Ala			
ctt Leu	gtt Val			
aac Asn 225	aat Asn			

WO 01/83701		PCT/US01/14394
	51/108	

48	96	144	192	240	288	336
aca Thr	gtt Val	ttc Phe	act Thr	atg Met 80	tac Tyr	tta Leu
cct Pro 15	ggt Gly	ttt Phe	tta Leu	tac Tyr	aga Arg 95	tac Tyr
ctt Leu	act Thr 30	gta Val	tca Ser	atg Met	ttt Phe	ttc Phe 110
gca Ala	tac Tyr	act Thr 45	aca Thr	tac Tyr	gta Val	gaa Glu
att Ile	gat Asp	ser	aaa Lys 60	cat His	act Thr	tgt Cys
gtt Val	agt Ser	gca Ala	tgg Trp	tgg Trp 75	cca Pro	ata Ile
agt Ser 10	gct Ala	tta Leu	aaa Lys	ttc Phe	tcg Ser 90	tta Leu
ggt Gly	gat Asp 25	cta Leu	gca Ala	gct Ala	gat Asp	tta Leu 105
ata Ile	ctt Leu	gct Ala 40	ser	att Ile	ggt Gly	cct Pro
ata Ile	gac Asp	gct Ala	gtt Val	ggt Gly	act Thr	gtt Val
ctg Leu	ggt Gly	aca Thr	aga Arg	act Thr 70	gaa Glu	aca Thr
tta cto Leu Leo 5	ggc Gly	gtt Val	gat Asp	gtt Val	att Ile 85	cta Leu
tta Leu	ggt Gly 20	tta Leu	aga Arg	ctt Leu	tgg Trp	tta Leu 100
aaa Lys	gca Ala	tgg Trp 35	gaa aga Glu Arg	ggt Gly	gta Val	tgg Trp
ggt Gly	gct Ala	ttt Phe	gtt Val 50	ser	gga G1y	gat Asp
atg Met 1	ttt Phe	tct Ser	ttt Phe	gta Val 65	aga Arg	att Ile

Figure 21

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384	432	480	528	576	624	672
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ctt Leu	gca Ala	tgg Trp 160	tgt Cys	tat Tyr	ggt Gly	tat Tyr
aaa Lys	gaa Glu	gct Ala	gca Ala 175	atg Met	aca Thr	atc Ile
aag Lys	ggt Gly	tta Leu	tct Ser	atg Met 190	ttc Phe	ctt Leu
ttt Phe 125	atg Met	tgt Cys	aaa Lys	aca Thr	tat Tyr 205	aac Asn
tta Leu	tac Tyr 140	ggg G $1y$	gga Gly	aac Asn	ggt Gly	tta Leu 220
tca Ser	ggt Gly	att Ile 155	gaa Glu	tac Tyr	gta Val	aac Asn
ggc Gly	ttt Phe	att Ile	gga Gly 170	gct Ala	cct Pro	ctt Leu
gcc Ala	gtg Val	ttc Phe	gct Ala	tca Ser 185	tat Tyr	gct Ala
gtt Val 120	ctt Leu	gca Ala	tat Tyr	caa Gln	att Ile 200	tca Ser
aat Asn	atg Met 135	cct Pro	cta Leu	gtg Val	gcg Ala	gga Gly 215
act Thr	gtt Val	tgg Trp 150	gaa Glu	gct Ala	tgg Trp	ggt Gly
gca Ala	ctt Leu	gct Ala	tat Tyr 165	cct Pro	ggt	gac Asp
gct Ala	tct Ser	gca Ala	att Ile	agt Ser 180	ttt Phe	ggt Gly
gct Ala 115	ggt Gly	atg Met	atg Met	gca Ala	gtc Val 195	atg Met
ctt Leu	gtt Val 130	att Ile	tat Tyr	aca Thr	atc Ile	ctg Leu 210
att Ile	cta Leu	gga G1 <u>y</u> 145	gta Val	aat Asn	att Ile	tac Tyr

Figure 2:

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720	750
rt tta att ata tgg y Leu Ile Ile Trp 240	
ttt ggt Phe Gly 235	
cta t Leu P	gct Ala 250
att Ile	aat Asn
aag Lys	tct Ser
aac Asn	tct Ser
gtt Val 230	gaa G1u
ttt Phe	aaa Lys 245
gac Asp	gtt Val
gct Ala	gct Ala
ctt Leu	gtt Val
ac sn 25	at

			54/108			
48	96	144	192	240	288	336
aca Thr	gtt Val	ttc Phe	act	atg Met 80	tac Tyr	tta Leu
cct Pro 15	ggt Gly	ttt Phe	tta Leu	tac Tyr	aga Arg 95	tac Tyr
ctt Leu	act Thr 30	gta Val	tca Ser	atg Met	ttt Phe	ttc Phe 110
gca Ala	tac Tyr	act Thr 45	aca Thr	tac Tyr	gta Val	gaa Glu
att Ile	gat Asp	tct Ser	aaa Lys 60	cat His	act Thr	tgt Cys
gtt Val	agt Ser	gca Ala	tgg Trp	tgg Trp 75	cca Pro	ata Ile
agt Ser 10	gct Ala	tta Leu	aaa Lys	ttc Phe	tcg Ser 90	ttg Leu
ggt Gly	gat Asp 25	cta Leu	gca Ala	gct Ala	gat Asp	cta Leu 105
tta Leu	ctt Leu	gct Ala 40	tct Ser	att Ile	ggt Gly	cct Pro
ata Ile	gac Asp	gct Ala	gtt Val 55	ggt Gly	act Thr	gtt Val
ctg Leu	ggt Gly	act Thr	aga Arg	act Thr 70	gag Glu	aca Thr
tta Leu 5	ggt Gly	gtt Val	gat Asp	gtt Val	att Ile 85	cta Leu
tta Leu	ggt Gly 20	tta Leu	aga Arg	ctt Leu	tgg Trp	tta Leu 100
aaa Lys	gca Ala	tgg Trp 35	gaa Glu	ggt Gly	gta Val	tgg Trp
ggt Gly	gct Ala	ttt Phe	gtt Val 50	tcg Ser	ggg G $1Y$	gat Asp
atg Met 1	ttt Phe	tct Ser	ttt Phe	gta Val 65	aga Arg	att Hle

Figure 22

			55/108			
384	432	480	8	9 /	24	72
m ·	4	4	52	57	62,	67
tta Leu	gca Ala	tgg Trp 160	tgt Cys	tat Tyr	ggt Gly	tat Tyr
aaa Lys	gag Glu	gct Ala	gca Ala 175	atg Met	aca Thr	atc Ile
aag Lys	ggt Gly	tta Leu	gct Ala	atg Met 190	ttc	ctt Leu
ttt Phe 125	atg Met	tgt Cys	aag Lys	aca Thr	tat Tyr 205	aac Asn
ctg Leu	tac Tyr 140	ggg G $1 \rm Y$	ggc $_{ m G1Y}$	aac Asn	ggt Gly	tta Leu 220
ggc Gly	ggt Gly	att Ile 155	gaa Glu	tac Tyr	gta Val	aac Asn
gct Ala	ttt Phe	gtt Val	gga G1Y 170	gct Ala	cct Pro	ctt Leu
gct Ala	gtg Val	ttc Phe	gct Ala	tca Ser 185	tat Tyr	gct Ala
gtt Val 120	ctt	gca Ala	tgg Trp	caa Gln	att Ile 200	tca Ser
aat Asn	atg Met 135	ggt Gly	cta Leu	gtg Val	gca Ala	gga G1 <u>Y</u> 215
. aca . Thr	gtt Val	tgg Trp 150	gaa Glu	gct Ala	tgg Trp	ggt Gly
gca Ala	ctt. Leu	gct Ala	tat Tyr 165	cct	ggt Gly	gac Asp
gct Ala	tct Ser	aac Asn	att Ile	agt Ser 180	ttt Phe	ggt Gly
gct Ala 115	ggt Gly	atg Met	atg Met	gca Ala	atc Ile 195	atg Met
ctt	gtt Val 130	att Ile	tac Tyr	act Thr	atc Ile	cta Leu 1210
att Ile	ttg Leu	gga G1y 145	gta Val	aat Asn	ata Ile	tac Tyr

Figure 22

720

tgg Trp 240	
ata Ile	
att Ile	
tta Leu	
ggt Gly	
ttt Phe 235	•
cta Leu	gct Ala 250
aat Asn	aat Asn
aag Lys	tct Ser
aac Asn	tat Ser
gtt Val 230	gaa Glu
ttt Phe	aaa Lys 245
gac Asp	gtt Val
gct Ala	gct Ala
ctt Leu	gtt Val
aac Asn 225	aat Asn

WO 01/83	9701		57/108			1 C 1/ USU 1/ 14.
48	96	144	192	240	288	336
cgg ata tta ggt agt gtt att gca ctt cct aca Arg Ile Leu Gly Ser Val Ile Ala Leu Pro Thr 10	ggt gac ctt gat gct agt gat tac act ggt gtt Gly Asp Leu Asp Ala Ser Asp Tyr Thr Gly Val 25	aca gct gct cta tta gca tct act gta ttt ttc Thr Ala Ala Leu Leu Ala Ser Thr Val Phe 40	aga gtt tct gca aaa tgg aaa aca tca tta act Arg Val Ser Ala Lys Trp Lys Thr Ser Leu Thr 55	act ggt att gct ttc tgg cat tac atg tat atg Thr Gly Ile Ala Phe Trp His Tyr Met Tyr Met 70	gaa act ggt gat tcg cca act gta ttt aga tac Glu Thr Gly Asp Ser Pro Thr Val Phe Arg Tyr 90	aca gtt cct tta tta ata tgt gaa ttc tac tta Thr Val Pro Leu Leu Ile Cys Glu Phe Tyr Leu 105
atg ggt aaa tta tta c Met Gly Lys Leu Leu A 1	ttt gct gca ggt ggc g Phe Ala Ala Gly Gly G	tct ttt tgg tta gtt a Ser Phe Trp Leu Val T 35	ttt gtt gaa aga gat a Phe Val Glu Arg Asp A 50	gta tct ggt ctt gtt a Val Ser Gly Leu Val T 65	aga gga gta tgg att g Arg Gly Val Trp Ile G 85	att gat tgg tta cta a Ile Asp Trp Leu Leu T

Figure 23

WO 01/83701		PCT/US01/14394
	58/108	

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384	432	480	528	576	624	672
				-,		
tta Leu	gca Ala	tgg Trp 160	tgt Cys	tat Tyr	ggt Gly	tat Tyr
aaa Lys	gaa Glu	gct Ala	gca Ala 175	atg Met	aca Thr	atc Ile
aag Lys	ggt Gly	tta Leu	tct Ser	atg Met 190	ttc Phe	ctt Leu
ttt Phe 125	atg Met	tgt Cys	aaa Lys	aca Thr	tat Tyr 205	aac Asn
tta Leu	tac Tyr 140	999 G1 <u>y</u>	gga G1y	aac Asn	ggt Gly	tta Leu 220
tca Ser	ggt Gly	att Ile 155	gaa Glu	tac Tyr	gta Val	aac Asn
gga Gly	ttt Phe	att Ile	gga Gly 170	gct Ala	cct Pro	ctt Leu
gct Ala	gtg Val	ttc Phe	gct Ala	tca Ser 185	tat Tyr	gct Ala
gtt Val 120	ctt Leu	gca Ala	tgg Trp	caa Gln	att Ile 200	tca Ser
aat Asn	atg Met 135	cct Pro	cta Leu	gtg Val	gcg Ala	gga G1Y 215
act Thr	gtt Val	tgg Trp 150	gaa Glu	gct Ala	tgg Trp	ggt Gly
gca Ala	ctt Leu	gca Ala	tat Tyr 165	cct Pro	ggt Gly	gac Asp
gct Ala	tct Ser	gct Ala	att Ile	agt Ser 180	gtt Val	ggt Gly
gct Ala 115	ggt Gly	atg Met	atg Met	gca Ala	atc Ile 195	atg Met
ctt Leu	gtt Val 130	atc Ile	tac Tyr	act Thr	atc Ile	ctg Leu 210
att Ile	cta Leu	gga Gly 145	gta Val	aat Asn	atc Ile	tac Tyr

Figure 23

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720	750
att ata tgg Ile Ile Trp 240	
tta Leu	
ggt Gly	
ttt Phe 235	
cta Leu	gct Ala 250
att Ile	aat Asn
aag Lys	tct Ser
aac Asn	tct Ser
gtt. Val 230	gaa Glu
ttt Phe	aaa Lys 245
gac Asp	gtt Val
gct Ala	gct Ala
ctt Leu	gtt Val
ac sn 25	at

			·			
48	96	144	192	240	. 588	336
٠.	•					
aca Thr	gtt Val	ttc Phe	act Thr	atg Met 80	tac Tyr	tta Leu
cct Pro 15	ggt Gly	ttt Phe	tta Leu	tac Tyr	aga Arg 95	tac Tyr
ctt Leu	act Thr 30	gta Val	tca Ser	atg Met	ttt Phe	ttc Phe 110
gca Ala	tac Tyr	act Thr 45	aca Thr	tac Tyr	gta Val	gaa Glu
att Ile	gat Asp	tct Ser	aaa Lys 60	cat His	act Thr	tgt Cys
gtt Val	agt Ser	gca Ala	tgg Trp	tgg Trp 75	cca Pro	ata Ile
agt Ser 10	gct Ala	tta Leu	aaa Lys	ttc Phe	tcg Ser 90	tta Leu
ggt Gly	gat Asp 25	cta Leu	gca Ala	gct Ala	gat Asp	tta Leu 105
tta Leu	ctt Leu	gct Ala 40	tct Ser	att Ile	${ t ggt}$	cct Pro
ata Ile	gac Asp	gct Ala	gtt Val 55	ggt Gly	act	gtt Val
ctg Leu	ggt Gly	aca Thr	aga Arg	act Thr 70	gaa Glu	aca Thr
tta Leu 5	ggc Gly	gtt Val	gat Asp	gtt Val	att Ile 85	cta Leu
tta Leu	ggt Gly 20	tta Leu	aga Arg	ctt Leu	tgg Trp	tta Leu 100
aaa Lys	gca Ala	tgg Trp 35	gaa Glu	ggt Gly	gta Val	tgg Trp
ggt Gly	gct Ala	ttt Phe	gtt Val 50	tct Ser	gga Gly	gat Asp
atg Met 1	ttt Phe	tct Ser	ttt Phe	gta Val 65	aga Arg	att Ile

Figure 24

432	480	528	576	624	672
gca Ala	tgg Trp 160	tgt Cys	gct Ala	ggt Gly	tat Tyr
gaa Glu	gct Ala	gca Ala 175	atg Met	aca Thr	att Ile
ggt Gly	tta Leu	tct Ser	atg Met 190	ttc Phe	ctt Leu
atg Met	tgt Cys	aaa Lys	aca Thr	tat Tyr 205	aac Asn
tac Tyr 140	999 G1y	gga ${ t G1Y}$	aac Asn	ggt Gly	tta Leu 220
ggt Gly	att Ile 155	gaa Glu	tac Tyr	gta Val	aac Asn
ttt Phe	att Ile	gga Gly 170	gct Ala	cct Pro	ctt Leu
gtg Val	ttc Phe	gct Ala	tca Ser 185	tat Tyr	gct Ala
ctt Leu	gca Ala	tat Tyr.	caa Gln	att Ile 200	tca Ser
atg Met 135	cct Pro	cta Leu	gtt Val	gca Ala	gga G1y 215
gtt Val	tgg Trp 150	gaa Glu	tag Ser	tgg Trp	ggt Gly
ctt Leu	gct Ala	tat Tyr 165	cct Pro	ggt Gly	gac Asp
tct Ser	gca Ala	att Ile	agt Ser 180	ttc Phe	ggt. Gly
ggt Gly	atg Met	atg Met	gca Ala	gtc Val 195	atg Met
gtt Val 130	att Ile	tac Tyr	act Thr	ata Ile	cta Leu 210
cta Leu	gga G1 <u>y</u> 145	gta Val	aat Asn	atc Ile	tac Tyr
	gtt ggt tct ctt gtt atg ctt gtg ttt ggt tac atg ggt gaa gca 43 Val Gly Ser Leu Val Met Leu Val Phe Gly Tyr Met Gly Glu Ala 130	a gtt ggt tct ctt gtt atg ctt gtg ttt ggt tac atg ggt gaa gca 4 u Val Gly Ser Leu Val Met Leu Val Phe Gly Tyr Met Gly Glu Ala 130 a att atg gca gct tgg cct gca ttc att att ggg tgt tta gct tgg y Ile Met Ala Ala Trp Pro Ala Phe Ile Ile Gly Cys Leu Ala Trp 5 150	gtt ggt tct ctt gtt atg ctt gtg ttt ggt tac atg ggt gaa gca 4 Val Gly Ser Leu Val Met Leu Val Phe Gly Tyr Met Gly Glu Ala 130  att atg gca gct tgg cct gca ttc att att ggg tgt tta gct tgg 4 Ile Met Ala Ala Trp Pro Ala Phe Ile Ile Gly Cys Leu Ala Trp 160  tac atg att tat gaa cta tat gct gga gaa gga aaa tct gca tgt Tyr Met Ile Tyr Glu Leu Tyr Ala Gly Glu Gly Lys Ser Ala Cys 175  Tyr Met Ile Tyr Glu Leu Tyr Ala Gly Glu Gly Lys Ser Ala Cys 175	yal Gly Ser Leu Val Met Leu Val Phe Gly Tyr Met Gly Glu Ala 130  att atg gca gct tgg cct gca ttc att att ggg tgt tta gct tgg Ile Met Ala Ala Trp Pro Ala Phe Ile Ile Gly Cys Leu Ala Trp Is atg att tat gaa cta tat gct gga gaa gga aaa tct gca tgt Tyr Met Ile Tyr Glu Leu Tyr Ala Gly Glu Gly Lys Ser Ala Cys 175  act gca agt cct tcg gtt caa tca gct tac aac aca atg atg gct Thr Ala Ser Pro Ser Val Gln Ser Ala Tyr Asn Thr Met Met Ala 180  185	9tt ggt tet ett gtt atg ett gtg ttt ggt tac atg ggt gaa gea Val Gly Ser Leu Val Met Leu Val Phe Gly Tyr Met Gly Glu Ala 135  att atg gea get tgg ect gea tte att att ggg tgt tta get tgg 160 met Ala Ala Trp Pro Ala Phe Ile Ile Gly Cys Leu Ala Trp 160 met atg aaa eta tat get gaa gaa gaa aaa tet gea tgt Tyr Met Ile Tyr Glu Leu Tyr Ala Gly Glu Gly Lys Ser Ala Cys 175 met gea agt eet teg gtt eaa tea get tac aac aca atg atg get 5 act gea agt eet teg gtt eaa tea get tac aac aca atg atg get 5 act gea agt eet teg gtt eaa tea get tac aac aca atg atg get 5 act gra gte tte ggt tgg gea att tat eet get ggt tat tee eagt tat ea get il 190 ata get atg tee Ala Ila Tyr Asn Thr Met Met Ala Ser Pro Ser Val Gln Ser Ala Tyr Asn Thr Met met Ala ata gte tte ggt tgg gea att tat eet gta ggt tat tte aca ggt Ile Val Phe Gly Trp Ala Ile Tyr Pro Val Gly Tyr Phe Thr Gly 195 lie Val Phe Gly Trp Ala Ile Tyr Pro Val Gly Tyr Phe Thr Gly 195 lie Val Phe Gly Trp Ala Ile Tyr Pro Val Gly Tyr Phe Thr Gly 195

Figure 24

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720	750
tgg Trp 240	
ata Ile	
att Ile	
tta Leu	
ggt Gly	
ttt Phe 235	
cta Leu	gct Ala 250
att Ile	aat Asn
aag Lys	tct Ser
aac Asn	tct Ser
gtt Val 230	gaa Glu
ttt Phe	aaa Lys 245
gac Asp	gtt Val
gct Ala	gct Ala
ctt	gtt Val
25 25 25	at sn

48	96	144	192	. 240	2 8 8	336
ggt aaa tta tta ctg ata tta ggt agt gtt att gca cít cct aca Gly Lys Leu Leu Leu Ile Leu Gly Ser Val Ile Ala Leu Pro Thr 5	gct gca ggt ggt gac ctt gat gct agt gat tac act ggt gtt Ala Ala Gly Gly Asp Leu Asp Ala Ser Asp Tyr Thr Gly Val 20	ttt tgg tta gtt act gct tta tta gca tct act gta ttt ttc Phe Trp Leu Val Thr Ala Ala Leu Leu Ala Ser Thr Val Phe Phe 35	gtt gaa aga gat aga gtt tct gca aaa tgg aaa aca tca tta act Val Glu Arg Asp Arg Val Ser Ala Lys Trp Lys Thr Ser Leu Thr 50	tct ggt ctt gtt act ggt att gct ttc tgg cat tac atg tac atg Ser Gly Leu Val Thr Gly Ile Ala Phe Trp His Tyr Met Tyr Met 75	ggg gta tgg att gaa act ggt gat tcg cca act gta ttt aga tac Gly Val Trp Ile Glu Thr Gly Asp Ser Pro Thr Val Phe Arg Tyr 90	gat tgg tta cta aca gtt cct cta tta ata tgt gaa ttc tac tta Asp Trp Leu Leu Thr Val Pro Leu Leu Ile Cys Glu Phe Tyr Leu 100
atg Met · 1	ttt Phe	tct Ser	ttt Phe	gta Val 65	aga Arg	att Ile

Figure 25

		, •				
384	432	480	528	576	624	672
c ctt gct gct act aat gtt gcc ggc tca tta ttt aag aaa ctt e Leu Ala Ala Ala Thr Asn Val Ala Gly Ser Leu Phe Lys Lys Leu 115	a gtt ggt tct ctt gtt atg ctt gtg ttt ggt tac atg ggt gaa gca 1 Val Gly Ser Leu Val Met Leu Val Phe Gly Tyr Met Gly Glu Ala 130	ga att atg gca gct tgg cct gca ttc att att ggg tgt tta gct tgg ly ile Met Ala Ala Trp Pro Ala Phe ile ile Gly Cys Leu Ala Trp 150	a tac atg att tat gaa cta tat gct gga gaa gga aaa tct gca tgt   Tyr Met Ile Tyr Glu Leu Tyr Ala Gly Glu Gly Lys Ser Ala Cys 170	c act gca agt cct tcg gtt caa tca gct tac aac aca atg atg gct n Thr Ala Ser Pro Ser Val Gln Ser Ala Tyr Asn Thr Met Met Ala 180	tc ata gtc ttc ggt tgg gca att tat cct gta ggt tat ttc aca ggt le Ile Val Phe Gly Trp Ala Ile Tyr Pro Val Gly Tyr Phe Thr Gly 205	cta atg ggt gac ggt gga tca gct ctt aac tta aac ctt att tat Fleu Met Gly Asp Gly Gly Ser Ala Leu Asn Leu Asn Leu Ile Tyr 210
att Ile	cta Leu	6 0 4	gta Val	aat Asn	ø ⊢i	tac Tyr

Figure 25

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720	750
ggt tta att ata tgg Gly Leu Ile Ile Trp 240	
cta ttt	gct
Leu Phe	Ala
235	250
att	aat
Ile	Asn
aag	tct
Lys	Ser
aac	tct
Asn	Ser
gtt Val 230	gaa Glu
ttt Phe	aaa Lys 245
gac	gtt
Asp	Val
gct	gct
Ala	Ala
ctt	gct
Leu	Ala
aac Asn 225	aat Asn

48	96	144	192	240	288	336
				12.0		
aca Thr	gtt Val	ttc Phe	act Thr	atg Met 80	tac Tyr	tta Leu
cct Pro 15	ggt Gly	ttt Phe	tta Leu	tat Tyr	aga Arg 95	tac Tyr
ctt Leu	act Thr 30	gta Val	tca Ser	atg Met	ttt Phe	ttc Phe 110
gca Ala	tac Tyr	act Thr 45	aca Thr	tac Tyr	gta Val	gaa Glu
att	gat Asp	tct Ser	aaa Lys 60	cat His	act Thr	tgt Cys
gtt Val	agt Ser	gca Ala	tgg Trp	tgg Trp 75	cca Pro	ata Ile
agt Ser 10	gct Ala	tta Leu	ааа Lys	ttc Phe	tcg Ser 90	tta Leu
ggt Gly	gat Asp 25	tta Leu	gca Ala	gct Ala	gat Asp	tta Leu 105
tta Leu	ctt Leu	gct Ala 40	tct Ser	att Ile	ggt Gly	cct Pro
ata Ile	gac Asp	gct Ala	gtt Val 55	ggt Gly	act Thr	gtt Val
ctg Leu	ggt Gly	act Thr	aga Arg	act Thr 70	gaa Glu	aca Thr
tta Leu 5	ggt Gly	gtt Val	gat Asp	gtt Val	att Ile 85	cta Leu
tta Leu	ggt Gly 20	tta Leu	aga Arg	ctt Leu	tgg Trp	tta Leu 100
aaa Lys	gca Ala	tgg Trp 35	gaa Glu	ggt Gly	gta Val	tgg Trp
ggt Gly	gct Ala	ttt Phe	gtt Val 50	tct Ser	999 G1 <u>y</u>	gat Asp
atg Met 1	ttt Phe	tct Ser	ttt Phe	gta Val 65	aga Arg	ata Ile

Figure 2

		•			,	
384	432	480	528	576	624	672
a tta s Leu	a gca 1 Ala	tgg a Trp 160	a tgt a Cys	rat Tyr	a ggt : Gly	tat Tyr
g aaa s Lys	t gaa Y Glu	a gct u Ala	t gca r Ala 175	g atg t Met 0	c aca e Thr	t att u Ile
ttt aag Phe Lys 125	atg ggt Met Gly	tgt tta Cys Leu	aaa tct Lys Ser	aca atg Thr Met 190	tat ttc Tyr Phe 205	aac ctt Asn Leu
tta t Leu P	tac a Tyr M 140	ggg t <sub>(</sub> Gļy C	gga a. Gly Ly	aac ao Asn Tl	ggt ta Gly Ty 2(	tta az Leu As 220
tca t Ser ]	ggt t	att g Ile ( 155	gaa g Glu (	tac a	gta g Val (	aac t Asn I
gga Gly	ttt	att Ile	gga Gly 170	gct Ala	cct	ctt Leu
t gct 1 Ala 0	gtg 1 Val	a ttc a Phe	gct Ala	tca Ser 185	tat Tyr	gca Ala
gt Va 12	g ctt t Leu 5	t gca o Ala	a tgg u Trp	g caa 1 Gln	g att a Ile 200	a tca Y Ser 5
ot aat or Asn	t at 1 Me 13	tgg cct Trp Pro 150	aa cta Lu Leu	it gtg .a Val	ıg gcg p Ala	rt gga Y Gly 215
gca ac Ala Th	ctt gt Leu Va	gca tç Ala Tı 15	tat ga Tyr Gl 165	cct gc Pro Al	ggt tg Gly Trj	gac ggt Asp Gly
gct g Ala A	tct Ser I	gct g Ala A	att t Ile 1	agt c Ser F 180	ttt g Phe G	ggt g Gly A
gcc Ala 115	ggt Gly	atg Met	atg Met	gca Ala	atc I1e 195	atg Met
ctt Leu	gtt val 130	a atc 7 Ile 5	tac Tyr	act Thr	atc Ile	ctt Leu
att Ile	ctt Leu	gga G1 <u>Y</u> 145	gta Val	aat Asn	atc Ile	tac Tyr

Figure 26

720	750
ata tgg Ile Trp 240	
att Ile	
tta Leu	
ggt Gly	
ttt Phe 235	
cta ttt Leu Phe 235	gct Ala 250
att Ile	aat Asn
aag Lys	tat Ser
aac Asn .	tct Ser
gtt Val 230	gaa Glu
ttt Phe	aaa Lys 245
gac Asp	gtt Val
gct Ala	gct Ala
ctt Leu	gtt Val
ac sn 25	at

			09/108			
						•
48	96	144	192	240	. 8	336
aca Thr	gtt Val	ttc Phe	act Thr	atg Met 80	tac Tyr	tta Leu
cct Pro 15	ggt Gly	ttt Phe	tta Leu	tat Tyr	aga Arg 95	tac Tyr
ctt Leu	act Thr 30	gta Val	tca Ser	atg Met	ttt Phe	ttc Phe 110
gca Ala	tac Tyr	act Thr 45	aca Thr	tac Tyr	gta Val	gaa Glu
att Ile	gat Asp	tct Ser	aaa Lys 60	cat His	act Thr	tgt Cys
gtt Val	agt Ser	gcg Ala	tgg Trp	tgg Trp 75	cca Pro	ata Ile
agt Ser 10	gct Ala	tta Leu	aaa Lys	ttc Phe	tcg Ser 90	tta Leu
ggt Gly	gat Asp 25	cta Leu	gca Ala	gct Ala	gat Asp	tta Leu 105
tta Leu	ctt Leu	gct Ala 40	tct Ser	att Ile	ggt Gly	cct Pro
ata Ile	gac Asp	gct Ala	gtt Val 55	ggt Gly	act Thr	gtt Val
ctg Leu	ggt Gly	aca Thr	aga Arg	act Thr 70	gaa Glu	aca Thr
tta Leu 5	ggc $_{ m G1Y}$	gtt Val	gat Asp	gtt Val	att Ile 85	cta Leu
aaa tta Lys'Leu	ggt Gly 20	tta Leu	aga Arg	ctt Leu	tgg Trp	tta cta Leu Leu 100
aaa Lys	gca Ala	tgg Trp 35	gaa Glu	ggt Gly	gta Val	tgg Trp
ggt Gly	gct Ala	ttt Phe	gtt Val 50	tct Ser	gga Gly	gat Asp
atg Met 1	ttt Phe	ser	ttt Phe	gta Val 65	aga Arg	att Ile

Figure 27

WO 01/83701		PCT/US01/14394
	70/108	

384	432	480	528	576	624	672
		· × ·				
ctt Leu	gca Ala	tgg Trp 160	tgt Cys	tat Tyr	ggt Gly	tat Tyr
aaa Lys	gaa Glu	gca Ala	gca Ala 175	atg Met	aca Thr	att Ile
aag Lys	ggt Gly	tta Leu	tct Ser	atg Met 190	ttc Phe	ctt Leu
ttt Phe 125	atg Met	tgt Cys	aaa Lys	aca Thr	tat Tyr 205	aac Asn
tta Leu	tac Tyr 140	gga Gly	gga Gly	aac Asn	ggt Gly	cta Leu 220
tca Ser	ggt Gly	gtt Val 155	gaa Glu	tac Tyr	cct gta Pro Val	Asn
ggc Gly	ttt	atc Ile	ggt Gly 170	gct Ala	cct gta Pro Val	cttjaat Leu Asn
gcc Ala	gtg Val	ttc Phe	gct Ala	tca Ser 185	tat Tyr	gct Ala
gtt Val 120	ctt Leu	gca Ala	tgg Trp	cag Gln	att Ile 200	tca Ser
aat Asn	atg Met 135	cct Pro	cta Leu	gta Val	gca Ala	gga Gly 215
act Thr	gtt Val	tgg Trp 150	gaa Glu	gct Ala	tgg Trp	ggt Gly
gca Ala	ctt Leu	gct Ala	tat Tyr 165	cct Pro	ggt Gly	gac Asp
gct Ala	tct Ser	gcg Ala	att Ile	agt Ser 180	gtt Val	ggt Gly
gct Ala 115	ggt Gly	atg Met	atg Met	gca Ala	atc Ile 195	atg Met
ctt Leu	gtt Val 130	ata Ile	tat Tyr	act Thr	atc Ile	cta Leu 210
att Ile	cta Leu	gga Gly 145	gta Val	aat Asn	atc Ile	tac Tyr

Figure 27

נ	7
	rigare

720	750
att ata tgg Ile Ile Trp 240	
t tta 7 Leu	
ttt ggt Phe Gly 235	
cta Leu	gct Ala 250
att Ile	aat Asn
aag Lys	tct
aac Asn	tct Ser
gtt Val 230	gaa Glu
ttt Phe	aaa Lys 245
gac Asp	gtt Val
gct Ala	gct Ala
ctt Leu	gtt Val
2 d d d	at sn

WO 01/83701		PCT/US01/14394
	72/108	

48	96	144	92	40	88	36
•			$\vdash$		73	m
d Ы	th H	ه ب	ъ И ~	d d	א ת	<b>๙</b> ว
tca Ser	gtt Val	ttt Phe	act Thr	atg Met 80	tat Tyr	cta Leu
cca Pro 15	ggt Gly	ttc Phe	ctt Leu	tac Tyr	aga Arg 95	tat Tyr
ctt Leu	gtt Val 30	gta Val	tca Ser	ctc Leu	ttt Phe	ttc Phe 110
gca Ala	act Thr	act Thr 45	act Thr	tat Tyr	gta Val	gag Glu
att Ile	gat Asp	gca Ala	aaa Lys 60	cat His	aca Thr	gtt Val
gct Ala	agt Ser	gcg Ala	tgg Trp	tgg Trp 75	cca Pro	atg Met
agt Ser 10	ata Ile	tta Leu	aag Lys	ttt Phe	aca Thr 90	caa Gln
ggt Gly	gat Asp 25	atg Met	gct Ala	gct Ala	gat Asp	tta Leu 105
tta Leu	cta Leu	ggt Gly 40	agc Ser	ata Ile	ggt Gly	cca Pro
ata Ile	gat Asp	gct Ala	gtc Val 55	ggt Gly	act Thr	gtt Val
ctg Leu	ggc Gly	aca Thr	caa Gln	act Thr 70	gat Asp	act Thr
tta Leu 5	ggt Gly	gtt Val	gac Asp	att Ile	ata Ile 85	tta Leu
tta Leu	gct Ala 20	ctg Leu	aga Arg	tta Leu	tgg Trp	cta Leu 100
aaa Lys	gct Ala	tgg Trp 35	gaa Glu	ggt Gly	gtt Val	tgg Trp
ggt Gly	gct	ttc Phe	gta Val 50	tct Ser	ggt Gly	gat Asp
atg Met 1	ttt Phe	tca Ser	ttt Phe	gta Val 65	aga Arg	att Ile

Figure 28

384	432	480	528	576	624	672
u d	ı) m	₩ O. O	odl	to ro	6	and at
ctt	gct Ala	tgg Trp 160	gta Val	aag Lys	ggt Gly	ata Ile
aag Lys	gaa Glu	ggt Gly	gct Ala 175	atg Met	gct Ala	ctt Leu
aag Lys	ggc Gly	gct Ala	gct Ala	atg Met 190	gct Ala	aac Asn
ttt Phe 125	gca Ala	atg Met	aag Lys	gca Ala	tat Tyr 205	tta Leu
tta Leu	ttt Phe 140	ggt Gly	ggt Gly	aat Asn	gga Gly	aac Asn 220
tca Ser	gga ${ t Gly}$	ctt Leu 155	gaa Glu	gct tac Ala Tyr	gct Ala	tca Ser
gct Ala	gct Ala	att Ile	ggt Gly 170	gct Ala	cct Pro	gct Ala
gct Ala	ggt Gly	ttc Phe	atg Met	tct Ser 185	tat Tyr	tac Tyr
gtt Val 120	tta Leu	gct Ala	cat His	aac Asn	att Ile 200	gta Val
agt Ser	atg Met 135	cct Pro	cta Leu	gtt Val	gca Ala	ggt Gly 215
aca Thr	gta Val	tta Leu 150	gag G1u	gct Ala	tgg Trp	gac Asp
tgt Cys	tta Leu	gta Val	tat Tyr 165	cct	gga Gly	ggt Gly
gct Ala	tca Ser	cct Pro	att Ile	agt Ser 180	att Ile	agt Ser
gct Ala 115	ggt Gly	gct Ala	atg Met	gca Ala	gtt Val 195	atg Met
ctt Leu	gct Ala 130	tta Leu	tac Tyr	act Thr	att Ile	cta Leu 210
att Ile	cta Leu	ggt Gly 145	tta Leu	agt Ser	att Ile	tac Tyr

Figure 28

720	753
t ttg atc att Y Leu Ile Ile 240	
ott ggt Phe Gly	
cta ttt Leu Phe 235	gct Ala
att Ile	aat Asn 250
aag Lys	tct Ser
aac Asn	tct Ser
gtt Val	gaa Glu
ttt Phe 230	aaa Lys
gac Asp	gtt Val 245
gct Ala	gct Ala
ctt Leu	gtt Val
Asn	aat Asn 1
tat Tyr 225	tgg Trp

P	CT.	Λī	Sn	1/	14	39	4

WO 01/83701			PCT/US01/14394
	75/108		

48	96	144	192	240	28.8	336
tca Ser	gtt Val	ttt Phe	act Thr	atg Met 80	tat Tyr	cta Leu
cca Pro 15	ggt Gly	ttc Phe	ctt Leu	tat Tyr	aga Arg 95	tat Tyr
ctt Leu	gtt Val 30	gtg Val	tca Ser	ctc Leu	ttc Phe	ttc Phe 110
gca Ala	act Thr	act Thr 45	act Thr	tat Tyr	gta Val	gag Glu
att Ile	gat Asp	gca Ala	aaa Lys 60	cat His	aca Thr	gtt Val
gct Ala	agt Ser	gcg Ala	tgg Trp	tgg Trp 75	cca Pro	atg Met
agt Ser 10	ata Ile	tta Leu	gag Glu	ttt Phe	acc Thr 90	caa Gln
ggt Gly	gat Asp 25	atg Met	gct Ala	gct Ala	gat Asp	tta Leu 105
tta Leu	cta Leu	ggt Gly 40	agc Ser	ata Ile	ggt Gly	cca Pro
ata Ile	gat Asp	gct Ala	gtc Val 55	ggt Gly	act Thr	gtt Val
ctg Leu	ggc Gly	aca Thr	caa Gln	act Thr 70	gat Asp	act Thr
tta Leu 5	${ t ggt}$	gtt Val	gac Asp	att Ile	ata Ile 85	tta Leu
tta Leu	gct Ala 20	ctg Leu	aga Arg	tta Leu	tgg Trp	tta Leu 100
aaa Lys	gct Ala	tgg Trp 35	gaa Glu	ggt Gly	gtt Val	tgg Trp
ggt Gly	gct Ala	ttc Phe	gta Val 50	tct Ser	ggt Gly	gat Asp
atg Met 1	ttt Phe	tca Ser	ttt Phe	gta Val 65	aga Arg	att Ile

Figure 29

384	432	480	528	576	624	672
att ctt gct gct tgt aca agt gtt gct gct tca ttt aag aag ctt 3 Ile Leu Ala Ala Cys Thr Ser Val Ala Ala Ser Leu Phe Lys Lys Leu 115	1) a;	gga tta gct cct gta tta cct gct ttc att att ggt atg gct gga tgg Gly Leu Ala Pro Val Leu Pro Ala Phe Ile Ile Gly Met Ala Gly Trp 145	tta tac atg att tat gag cta tat atg ggt gaa ggt aag gct gct gta Leu Tyr Met Ile Tyr Glu Leu Tyr Met Gly Glu Gly Lys Ala Ala Val 170	agt act gca agt cct gct gtt aac tct gca tac aac gca atg atg atg Ser Thr Ala Ser Pro Ala Val Asn Ser Ala Tyr Asn Ala Met Met Met 180	att att gtt gtt gga tgg gca att tat cct gct gga tat gct gct ggt Ile Ile Val Val Gly Trp Ala Ile Tyr Pro Ala Gly Tyr Ala Ala Gly 205	tac cta atg ggt ggc gaa ggt gta tac gct tca aac tta aac ctt ata 6 Tyr Leu Met Gly Glu Gly Val Tyr Ala Ser Asn Leu Asn Leu Ile 210

Figure 29

720	753
ttt ggt ttg atc att Phe Gly Leu Ile Ile 240	
cta Leu ] 235	gct Ala
att Ile	aat Asn 250
aag Lys	tct Ser
aac Asn	tct Ser
gtt Val	gaa G1u
ttt Phe 230	aaa Lys
gac Asp	gtt Val 245
gct Ala	gct Ala
ctt Leu	gtt Val
aac Asn	aat Asn
tat Tyr 225	tgg Trp

48	96	. 144	192	240	288	336
aaa tta tta ctg ata tta ggt agt gct att gca ctt cca tca Lys Leu Leu Leu Ile Leu Gly Ser Ala Ile Ala Leu Pro Ser 5	gct gct ggt ggc gat cta gat ata agt gat act gtt ggt gtt Ala Ala Gly Asp Leu Asp Ile Ser Asp Thr Val Gly Val 20	tgg ctg gtt aca gct ggt atg tta gcg gca act gtg ttc ttt Trp Leu Val Thr Ala Gly Met Leu Ala Ala Thr Val Phe Phe 35	gaa aga gac caa gtc agc gct aag tgg aaa act tca ctt act Glu Arg Asp Gln Val Ser Ala Lys Trp Lys Thr Ser Leu Thr 55	ggt tta att act ggt ata gcc ttt tgg cat tat ctc tat atg Gly Leu Ile Thr Gly Ile Ala Phe Trp His Tyr Leu Tyr Met 70	gtt tgg ata gac act ggt gat acc cca aca gta ttc aga tat Val Trp Ile Asp Thr Gly Asp Thr Pro Thr Val Phe Arg Tyr 90	tgg tta tta act gtt cca tta caa atg gtt gag ttc tat cta Trp Leu Leu Thr Val Pro Leu Gln Met Val Glu Phe Tyr Leu 100
atg ggt Met Gly 1	ttt gct Phe Ala	tca ttc Ser Phe	ttt gta Phe Val 50	gta tct Val Ser 65	aga ggt Arg Gly	att gat Ile Asp
•			· • •	J. F		- <del>-</del> • •

Figure 30

WO 01/83701		PCT/US01/14394
	79/108	

384	432	480	528	576	624	672
tta ttt aag aag ctt Leu Phe Lys Lys Leu 125	ttt gca ggc gaa gct Phe Ala Gly Glu Ala 140	ggt atg gct gga tgg Gly Met Ala Gly Trp 160	ggt aag gct gct gta Gly Lys Ala Ala Val 175	aac gca atg atg atg Asn Ala Met Met Met 190	ya tat gct gct ggt y Tyr Ala Ala Gly 205	ic cta aac ctt ata in Leu Asn Leu Ile 10
ct gct tca la Ala Ser	ggt gct gga tt Gly Ala Gly Ph 14	ttc att att gg Phe Ile Ile G] 155	g ggt gaa t Gly Glu 170	tct gca tac aac Ser Ala Tyr Asn 185	tat cct gct gga Tyr Pro Ala Gly	tac gct tca aac Tyr Ala Ser Asn 220
aat gtt Asn Val 120	atg tta Met Leu 135	cct gct Pro Ala	ag cta tat at lu Leu Tyr Me	t gtt aac a Val Asn	gca att Ala Ile 200	a ggt gta ta u Gly Val Ty 215
t gct tgt aca a Ala Cys Thr 5	t tca tta gta y Ser Leu Val	t cct gta tgg a.Pro Val Trp 150	att tat g Ile Tyr G 165	agt cct gc Ser Pro Al 180	: gtt gga tgg   Val Gly Trp	ggt ggc ga Gly Gly Gl
att ctt gct Ile Leu Ala 115	cta gct ggt Leu Ala Gly 130	gga tta gct Gly Leu Ala 145	tta tac atg Leu Tyr Met	agt act gca Ser Thr Ala	att att gtt Ile Ile Val	tac cta atg Tyr Leu Met 210
			•			

Figure 30

720	753
ttt ggt ttg atc att Phe Gly Leu Ile Ile 240	
cta ti Leu Pl 235	gct Ala
att Ile	aat Asn 250
aag Lys	tct Ser
aac Asn	tct Ser
gtt Val	gaa Glu
ttt Phe 230	ааа Lys
gac Asp	gtt Val 245
gct Ala	gct Ala
ctt Leu	gtt Val
aac Asn	aat Asn
tat Tyr 225	tgg Trp

wo	01/83701	
****	V1/02/VI	

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•			81/108			
48	96	144	192	240	7 88 8	336
tg ggt aaa tta tta ctg ata tta ggt agt gct att gcg ctt cca tca et Gly Lys Leu Leu Leu Ile Leu Gly Ser Ala Ile Ala Leu Pro Ser 5	ttt gct gct ggt ggc gat cta gat ata agt gat act gtt ggt gtt Phe Ala Ala Ala Gly Gly Asp Leu Asp Ile Ser Asp Thr Val Gly Val 25	ca ttc tgg ctg gtt acg gct ggt atg tta gcg gca act gta ttc ttt er Phe Trp Leu Val Thr Ala Gly Met Leu Ala Ala Thr Val Phe Phe 35	tt gta gaa aga gac caa gtc agc gct aag tgg aaa act tca ctt act ne Val Glu Arg Asp Gln Val Ser Ala Lys Trp Lys Thr Ser Leu Thr 50	ta tot ggt tta att act ggt ata gct ttt tgg cat tat ctc tac atg al Ser Gly Leu Ile Thr Gly Ile Ala Phe Trp His Tyr Leu Tyr Met 75	ya ggt gtt tgg ata gat act ggt gat aca cca aca gta ttt aga tat rg Gly Val Trp Ile Asp Thr Gly Asp Thr Pro Thr Val Phe Arg Tyr 90	ct gat tgg tta tta act gtt cca tta caa atg gtt gag ttc tat cta le Asp Trp Leu Leu Thr Val Pro Leu Gln Met Val Glu Phe Tyr Leu 100
atg Met 1	tt Ph	tca Ser	ttt Phe	gta Val 65	aga Arg	att Ile

Figure 31

PCT/US01/14394

WO 01/83701		PCT/US01/14394
	82/108	

384	432	480	528	576	624	672
·		·	_,	₹′		
ctt Leu	gct Ala	tgg Trp 160	gta Val	atg Met	ggt. Gly	ata Ile
aag Lys	gaa Glu	gga Gly	gct Ala 175	atg Met	gct Ala	ctc Leu
aag Lys	ggc Gly	gct Ala	gct Ala	atg Met 190	gct Ala	aac Asn
ttt Phe 125	gca Ala	atg Met	aag Lys	gca Ala	tat Tyr 205	tta Leu
tta Leu	tct Ser 140	ggt Gly	ggt Gly	aac Asn	gga Gl <u>y</u>	aac Asn 220
tca Ser	gga Gly	att Ile 155	gaa Glu	tac Tyr	gct Ala	tca Ser
gct Ala	gct Ala	att Ile	ggt Gly 170	gca Ala	cct Pro	gct Ala
gct Ala	ggt Gly	ttc Phe	atg Met	tct Ser 185	tat Tyr	tac Tyr
gtt Val 120	tta Leu	gct Ala	tat Tyr	aac Asn	att Ile 200	gta Val
agt Ser	atg Met 135	cct Pro	cta Leu	gtt Val	gca Ala	ggt Gly 215
aca Thr	gta Val	tta Leu 150	gag Glu	gct Ala	tgg Trp	gaa Glu
tgt Cys	ttg Leu	gta Val	tat Tyr 165	cct Pro	gga Gly	ggc Gly
gct Ala	tca Ser	cct Pro	att Ile	agt Ser 180	gtt Val	ggt Gly
gcc Ala 115	ggt Gly	gct Ala	atg Met	gca Ala	gtt Val 195	atg Met
ctt Leu	gct Ala 130	tta Leu	tac Tyr	act Thr	att Ile	cta Leu 210
att Ile	cta Leu	gga Gly 145	tta Leu	agt Ser	att Ile	tac Tyr

Figure 31

720	753
tc att le Ile 240	·
Вч	•
t Le	
ggt Gly	engliser en
ttt Phe	
cta ttt Leu Phe 235	gct Ala
att Ile	aat Asn 250
aag Lys	tct Ser
aac Asn	tct Ser
gtt Val	gaa Glu
ttt Phe 230	aaa Lys
gac Asp	gtt Val 245
ctt gct ga Leu Ala As	gtt gct Val Ala
ctt	gtt Val
aac Asn	aat Asn
tat Tyr 225	tgg Trp

			84/108			
48	96	144	192	240	2888	336
tta ctg ata tta ggt agt gct att gca ctt cca tca Leu Leu Ile Leu Gly Ser Ala Ile Ala Leu Pro Ser 5	ggt ggc gat cta gat ata agt gat act gtt ggt gtt Gly Gly Asp Leu Asp Ile Ser Asp Thr Val Gly Val 25	gtt aca gct ggt atg tta gcg gca act gtg ttc ttt Val Thr Ala Gly Met Leu Ala Ala Thr Val Phe . 40	gac caa gtc agc gct aag tgg aaa act tca ctt act Asp Gln Val Ser Ala Lys Trp Lys Thr Ser Leu Thr 55	att act ggt ata gct ttt tgg cat tat ctc tat atg Ile Thr Gly Ile Ala Phe Trp His Tyr Leu Tyr Met 70 70 80	ata gac act ggt gat acc cca aca gta ttc aga tat Ile Asp Thr Gly Asp Thr Pro Thr Val Phe Arg Tyr 85	tta act gtt cca tta caa atg gtt gag ttc tat cta Leu Thr Val Pro Leu Gln Met Val Glu Phe Tyr Leu 105
aaa tta Lys Leu	gct gct Ala Ala 20	tgg ctg Trp Leu 35	gaa aga Glu Arg	ggt tta Gly Leu	gtt tgg Val Trp	tgg tta Trp Leu 100
atg ggt a Met Gly I 1	ttt gct g Phe Ala A	tca ttc t Ser Phe 1	ttt gta g Phe Val G 50	gta tct g Val Ser G 65	aga ggt g Arg Gly V	att gat t Ile Asp T
						•

Figure 32

WO 01/8	3701		85/108			PCT/US01/
384	432	480	528	576	624	672
ctt gct gct tgt aca aat gtt gct gct tca tta ttt aag aag ctt Leu Ala Ala Cys Thr Asn Val Ala Ala Ser Leu Phe Lys Lys Leu 115	gct ggt tca tta gta atg tta ggt gct gga ttt gca ggc gaa gct Ala Gly Ser Leu Val Met Leu Gly Ala Gly Phe Ala Gly Glu Ala 130	tta gct cct gta tgg cct gct ttc att att ggt atg gct gga tgg Leu Ala Pro Val Trp Pro Ala Phe Ile Ile Gly Met Ala Gly Trp 150	tac atg att tat gag cta tat atg ggt gaa ggt aag gct gct gta Tyr Met Ile Tyr Glu Leu Tyr Met Gly Glu Gly Lys Ala Ala Val 175	t gca agt cct gct gtt aac tct gca tac aac gca atg atg gtg r Ala Ser Pro Ala Val Asn Ser Ala Tyr Asn Ala Met Met Val 180	t gtt gtt gga tgg gca att tat cct gct gga tat gct gct ggt e Val Val Gly Trp Ala Ile Tyr Pro Ala Gly Tyr Ala Ala Gly 195	a atg ggt ggc gaa ggt gta tac gct tca aac cta aac ctt ata u Met Gly Glu Gly Val Tyr Ala Ser Asn Leu Asn Leu Ile 0
att c Ile L	cta g Leu A	gga tta Gly Leu 145	tta tac Leu Tyr	agt act Ser Thr	att att Ile Ile	tac cta Tyr Leu 210

Figure 32

720	753
ttt ggt ttg atc att Phe Gly Leu Ile Ile 240	
cta ti Leu Pl 235	gct Ala
n att H n e	aat Asn 250
aag Lys	tct Ser
aac Asn	tct Ser
gtt Val	gaa Glu
ttt Phe 230	ааа Lys
gac Asp	gtt Val 245
gct Ala	gct Ala
ctt Leu	gtt Val
aac Asn	aat Asn
tat Tyr 225	tgg Trp

48	96	144	192	240	288	336
ggt aaa tta tta ctg ata tta ggt agt gct att gca ctt cca tca Gly Lys Leu Leu Leu Ile Leu Gly Ser Ala Ile Ala Leu Pro Ser 5	gct gct gct ggt ggc gat cta gat ata agt gat act gtt ggt gtt Ala Ala Ala Gly Gly Asp Leu Asp Ile Ser Asp Thr Val Gly Val 20	ttc tgg ctg gtt aca gct ggt atg tta gcg gca act gtg ttc ttt Phe'Trp Leu Val Thr Ala Gly Met Leu Ala Ala Thr Val Phe Phe 35	gta gaa aga gac caa gtc agc gct aag tgg aaa act tca ctt act Val Glu Arg Asp Gln Val Ser Ala Lys Trp Lys Thr Ser Leu Thr 50	tct ggt tta att act ggt ata gct ttt tgg cat tat ctc tat atg Ser Gly Leu Ile Thr Gly Ile Ala Phe Trp His Tyr Leu Tyr Met 70	ggt gtt tgg ata gac act ggt gat acc cca aca gta ttc aga tat Gly Val Trp Ile Asp Thr Gly Asp Thr Pro Thr Val Phe Arg Tyr 90	gat tgg tta tta act gtt cca tta caa atg gtt gag ttc tat cta Asp Trp Leu Leu Thr Val Pro Leu Gln Met Val Glu Phe Tyr Leu 100
atg g Met (	ttt g Phe A	tca t Ser 1	ttt g Phe 7	gta t Val 65	aga g Arg G	att g Ile Z

Figure 33

DOTOTION IN AND	0.4
PCT/US01/1439	74

WO 01/8	33701		88/108	<b>.</b>		PCT/US01/14
384	432	480	528	576	624	672
att ctt gct gct tgt aca agt gtt gct gct tca tta ttt aag aag ctt Ile Leu Ala Ala Cys Thr Ser Val Ala Ala Ser Leu Phe Lys Lys Leu 115	cta gct ggt tca tta gta atg tta ggt gct gga ttt gca ggc gaa gct Leu Ala Gly Ser Leu Val Met Leu Gly Ala Gly Phe Ala Gly Glu Ala 130	gga tta gct cct gta tta cct gct ttc att att ggt atg gct gga tgg Gly Leu Ala Pro Val Leu Pro Ala Phe Ile Ile Gly Met Ala Gly Trp 145	tta tac atg att tat gag cta tat atg ggt gaa ggt aag gct gct gta Leu Tyr Met Ile Tyr Glu Leu Tyr Met Gly Glu Gly Lys Ala Ala Val 175	gt act gca agt cct gct gtt aac tct gca tac aac gca atg atg atg er Thr Ala Ser Pro Ala Val Asn Ser Ala Tyr Asn Ala Met Met 180	att att gtt gtt gga tgg gca att tat cct gct gga tat gct gct ggt Ile Ile Val Val Gly Trp Ala Ile Tyr Pro Ala Gly Tyr Ala Ala Gly 200	tac cta atg ggt ggc gaa ggt gta tac gct tca aac tta aac ctt ata Tyr Leu Met Gly Gly Glu Gly Val Tyr Ala Ser Asn Leu Asn Leu Ile 210
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Figure 33

720	753
ttt ggt ttg atc att Phe Gly Leu Ile Ile 240	
cta t Leu 1 235	gct Ala
att Ile	aat Asn 250
aag Lys	tct Ser
aac Asn	tct Ser
gtt Val	gaa Glu
ctt Leu 230	aaa Lys
gac Asp	gtt Val 245
gct Ala	gct Ala
ctt Leu	gtt Val
aac Asn	aat Asn
tat Tyr 225	tgg Trp

48	96	144	192	240	288	336
			·			
tca Ser	gtt Val	tt Phe	act Thr	atg Met 80	tat Tyr	cta Leu
cca Pro 15	ggt Gly	ttc Phe	ctt Leu	tat Tyr	aga Arg 95	tat Tyr
ctt Leu	gtt Val 30	gtg Val	tca Ser	ctc Leu	ttc Phe	ttc Phe 110
gca Ala	act Thr	act Thr 45	act Thr	tat Tyr	gta Val	gag Glu
att Ile	gat Asp	gca Ala	aaa Lys 60	cat His	aca Thr	gtt Val
gct Ala	agt Ser	gcg Ala	tgg Trp	tgg Trp 75	cca Pro	gtg Val
agt Ser 10	ata Ile	tta Leu	aag Lys	ttt Phe	acc Thr 90	caa Gln
ggt Gly	gat Asp 25	atg Met	gct Ala	gct Ala	gat Asp	tta Leu 105
tta Leu	cta Leu	ggt Gly 40	agc Ser	ata Ile	ggt Gly	cca Pro
ata Ile	gat Asp	gct Ala	gtc Val 55	ggt Gly	act Thr	gtt Val
ctg Leu	ggc Gly	aca Thr	caa Gln	act Thr 70	gac Asp	act Thr
tta Leu 5	ggt Gly	gtt Val	gac Asp	att Ile	ata Ile 85	tta Leu
tta Leu	gct Ala 20	ctg Leu	aga Arg	tta Leu	tgg Trp	tta Leu 100
aaa Lys	gct Ala	tgg Trp 35	gaa Glu	ggt Gly	gtt Val	tgg Trp
ggt Gly	gct Ala	ttc Phe	gta Val 50	ser	ggt Gly	gat Asp
atg Met 1	ttt Phe	tca Ser	ttt Phe	gta Val 65	aga Arg	att Ile

Figure 34

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D	CT	/US01	1/1/	204
		LUOU.	/ 14	.374

WO 01/83701			PCT/US01/1
	01/108		

384	432	480	528	576	624	672
a ttt aag aag ctt u Phe Lys Lys Leu 125	t gca ggc gaa gct e Ala Gly Glu Ala 0	t atg gct gga tgg y Met Ala Gly Trp 160	c aag gct gct gta Y Lys Ala Ala Val 175	s gca atg atg n Ala Met Met Met 190	a tat gct gct ggt 7 Tyr Ala Ala Gly 205	tta aac ctt ata 1 Leu Asn Leu Ile )
st gct tca tta la Ala Ser Leu	gct gga tt Ala Gly Ph 14	c att att ggt le Ile Ile Gly 155	g ggt gaa ggc st Gly Glu Gly 170	it gca tac aac o Ala Tyr Asn 85	ıt cct gct gga r Pro Ala Gly	c gct tca aac r Ala Ser Asn 220
a agt gtt gct : Ser Val Ala 120	atg tta ggt .Met Leu Gly 135	cct gct ttc Pro Ala Phe )	r cta tat atg . Leu Tyr Met	gtt aac cct Val Asn Pro 185	gca att tat Ala Ile Tyr 200	ggt gta tac Gly Val Tyr 215
gct tgt aca Ala Cys Thr	tca tta gta Ser Leu Val	cct gta tta Pro Val Leu 150	att tat gag Ile Tyr Glu 165	agt cct gct Ser Pro Ala 180	gtt gga tgg Val Gly Trp	ggt ggc gaa Gly Gly Glu
att ctt gct Ile Leu Ala 115	cta gct ggt Leu Ala Gly 130	gga tta gct Gly Leu Ala 145	tta tac atg Leu Tyr Met	agt act gca Ser Thr Ala	att att gtt Ile Ile Val 195	tac cta atg Tyr Leu Met 210

Figure 34

720	753
O (b) (t)	
att Ile 24(	
atc Ile	
ttg Leu	
ggt Gly	
ttt Phe	
cta Leu 235	gct Ala
att Ile	aat Asn 250
aag Lys	tct Ser
aac Asn	tct Ser
gtt Val	gaa Glu
ttt Phe 230	aaa Lys
gac Asp	gtt Val 245
gct Ala	gct Ala
ctt Leu	gtt Val
aac Asn	aat Asn
tat Tyr 225	tgg Trp

WO 01/8	3701	•	93/108			PCT/US01/14394
48	9 9	144	192	240	288 8	336
tca Ser	gtt Val	ttt Phe	act Thr	atg Met 80	tat Tyr	cta Leu
cca Pro 15	ggt Gly	ttc Phe	ctt Leu	tac Tyr	aga Arg 95	tat Tyr
ctt Leu	gtt Val 30	gta Val	tca Ser	ctc Leu	ttt Phe	ttc Phe 110
gca Ala	act Thr	act Thr 45	act Thr	tat Tyr	gta Val	gag Glu
att Ile	gat Asp	gca Ala	aaa Lys 60	cat His	aca Thr	gtt Val
gct Ala	agt Ser	gcg Ala	tgg Trp	tgg Trp 75	cca Pro	atg Met
agt Ser 10	ata Ile	tta Leu	aag Lys	ttt Phe	aca Thr 90	caa Gln
ggt Gly	gat Asp 25	atg Met	gct Ala	gct Ala	gat Asp	tta Leu 105
tta Leu	cta Leu	ggt Gly 40	agc Ser	ata Ile	ggt Gly	сса Рго
		_				

gtc Val 55

caa Gln

gac Asp

aga Arg

gaa Glu

gta Val

Phe

ttt

50

ggt Gly

act Thr 70

Ile

tta

ggt Gly

gta Val 65

tct Ser

att

act Thr

gat Asp

tgg Trp

gtt Val

ggt Gly

aga Arg

ata Ile 85

gat

ggc Gly

ggt Gly

gct Ala

gct Ala

gct Ala

ttt

Phe

20

gct Ala

aca

gtt<sub>.</sub> Val

ctg Leu

tgg

Trp 35

Phe

tca Ser

Ile ata

ctg Leu

tta Leu

aaa Lys

ggt Gly

atg Met 1

tta Leu 5

35 Figure

gtt Val

tta Leu

tta

tgg Trp

att gat Ile Asp

act Thr

Leu 100

	$\mathbf{n}$	/83701	
wii		/X 1 / III	

04	/1	ΛQ

P	CT.	/IIS	01	/14	1394	

384	432	480	528	576	624	672
ctt Leu	gct Ala	tgg Trp 160	gta Val	aag Lys	ggt Gly	ata Ile
aag Lys	gaa Glu	gga $_{ m G1Y}$	gct Ala 175	atg Met	gct Ala	ctt Leu
aag Lys	ggc $_{ m G1Y}$	gct Ala	gct Ala	atg Met 190	gct Ala	aac Asn
ttt Phe 125	gca Ala	atg Met	aag Lys	gca Ala	tat Tyr 205	tta Leu
tta Leu	ttt Phe 140	ggt Gly	ggt Gly	aac Asn	gga Gly	aac Asn 220
tca Ser	gga $_{ m G1Y}$	att Ile 155	gaa Glu	tac Tyr	gct Ala	tca Ser
gct Ala	gct Ala	att Ile	ggt Gly 170	gca Ala	cct Pro	gct Ala
gct Ala	ggt Gly	ttc Phe	atg Met	tct Ser 185	tat Tyr	tac Tyr
gtt Val 120	tta Leu	gct Ala	cat His	aac Asn	att Ile 200	gta Val
agt Ser	atg Met 135	cct Pro	cta Leu	gtt Val	gca Ala	ggt Gly 215
aca Thr	gta Val	tta Leu 150	gag G1u	gct Ala	tgg Trp	gac
tgt Cys	tta Leu	gta Val	tat Tyr 165	cct Pro	gga Gly	ggt Gly
gct Ala	tca Ser	cct Pro	att Ile	agt Ser 180	att Ile	agt Ser
gct Ala 115	ggt Gly	gct Ala	atg Met	gca Ala	gtt Val 195	atg Met
ctt Leu	gct Ala 130	tta Leu	tac Tyr	act Thr	att Ile	cta Leu 210
att Ile	cta Leu	ggt Gly 145	tta Leu	agt Ser	att Ile	tac Tyr

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ħά
gct Ala
aat Asn 250
tct Ser
tct Ser
gaa Glu
ааа Lys
gtt Val 245
gct Ala
gtt Val
aat Asn
tgg Trp

48	96	144	192	240	28	336
		,				
tca Ser	gtt Val	ttt Phe	act Thr	atg Met 80	tat Tyr	cta Leu
cca Pro 15	ggt Gly	ttc Phe	ctt Leu	tat Tyr	aga Arg 95	tat Tyr
ctt Leu	gtt Val 30	gtg Val	tca Ser	ctc Leu	ttc Phe	ttc Phe 110
gca Ala	act Thr	act Thr 45	act Thr	tat Tyr	gta Val	gag Glu
att Ile	gat Asp	gca Ala	aaa Lys 60	cat His	aca Thr	gtt Val
gct Ala	agt Ser	gcg Ala	tgg Trp	tgg Trp 75	cca Pro	atg Met
agt Ser 10	ata Ile	tta Leu	aag Lys	ttt Phe	acc Thr 90	caa Gln
ggt Gly	gat Asp 25	atg Met	gct Ala	gct Ala	gat Asp	tta Leu 105
tta Leu	cta Leu	ggt Gly 40	agc Ser	ata Ile	ggt Gly	cca Pro
ata Ile	gat Asp	gct Ala	gtc Val 55	ggt Gly	act Thr	gtt Val
ctg Leu	ggc Gly	aca Thr	caa Gln	act Thr 70	gat Asp	act Thr
tta Leu 5	ggt Gly	gtt Val	gac Asp	att Ile	ata Ile 85	tta Leu
tta Leu	gct Ala 20	ctg Leu	aga Arg	tta Leu	tgg Trp	tta Leu 100
aaa Lys	gct Ala	tgg Trp 35	gaa Glu	ggt Gly	gtt Val	tgg Trp
ggt Gly	gct Ala	ttc Phe	gta Val 50	tct Ser	ggt Gly	gat Asp
atg Met 1	ttt Phe	tca Ser	ttt Phe	gta Val 65	aga Arg	att Ile

Figure 36

384	432	480	528	576	624	672
d ctt	a gct 1 Ala	a tgg 7 Trp 160	gta val	atg : Met	ggt Gly	ata 1 Ile
g aag s Lys	c gaa y Glu	t gga a Gly	t gct a Ala 175	g atg t Met 0	t gct a Ala	c ctt n Leu
ttt aag Phe Lys 125	gca ggc Ala Gly	atg gct Met Ala	aag gct Lys Ala	gca atg Ala Met 190	tat gct Tyr Ala 205	tta aac Leu Asn
tta t Leu P	ttt g Phe A 140	ggt a Gly M	ggt a Gly L	aac g Asn A	gga t Gly T	aac t Asn L
tca Ser	gga Gly	att Ile 155	gaa Glu	tac Tyr	gct g	tca Ser
gct Ala	gct Ala	att Ile	ggt Gly 170	gca Ala	cct Pro	gct Ala
t gct 1 Ala )	a ggt 1 Gly	ttc Phe	s atg Met	tct Ser 185	tat Tyr	a tac 1 Tyr
rt gtt r Val 120	g tta it Leu 5	t gct o Ala	a tat u Tyr	t aac 1 Asn	a att a Ile 200	gt Va
ca agt hr Ser	ta atg al Met 135	tta cct Leu Pro 150	ag cta lu Leu	st gtt La Val	tgg gca Trp Ala	aa ggc Lu Gly 215
tgt ac Cys Th	tta gt Leu Va	gta ti Val Lé	tat ga Tyr Gl 165	cct gc Pro Al	gga tç Gly Tı	ggc ga Gly Gl
gct Ala	tca Ser	cct	att Ile	agt Ser 180	gtt Val	ggt Gly
gct Ala 115	ggt Gly	gct Ala	atg Met	gca Ala	gtt Val 195	atg. Met
c ctt e Leu	a gct 1 Ala 130	a tta 7 Leu 5	a tac 1 Tyr	act Thr	att Ile	cta Leu 210
att Ile	cta Leu	gga G1 <u>Y</u> 145	cta Leu	agt Ser	att Ile	tac Tyr

Figure 36

720	753
ttt ggt ttg atc att Phe Gly Leu Ile Ile 240	
cta t Leu P 235	gct Ala
att Ile	aat Asn 250
aag Lys	tct Ser-
aac Asn	tct Ser
gtt Val	gaa Glu
ttt Phe 230	aaa Lys
gac Asp	gtt Val 245
gct Ala	gct Ala
ctt Leu	gtt Val
aac Asn	aat Asn
tat Tyr 225	tgg Trp

Figure 3

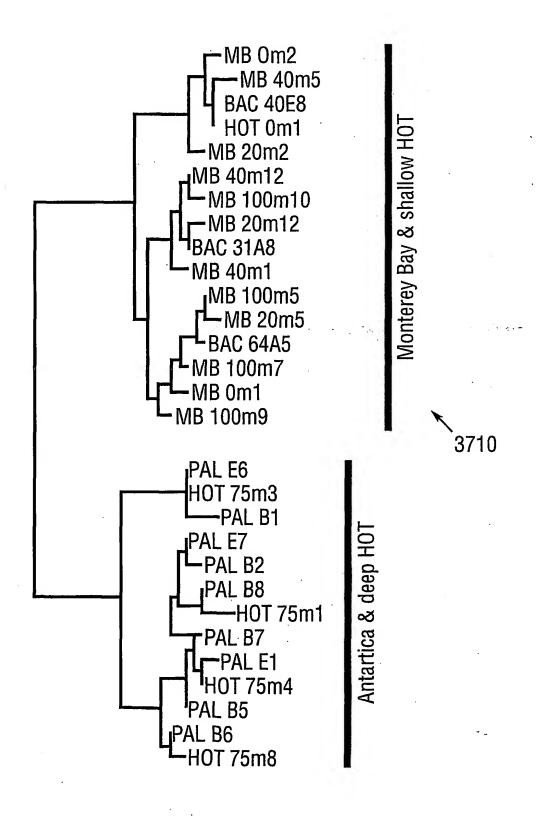
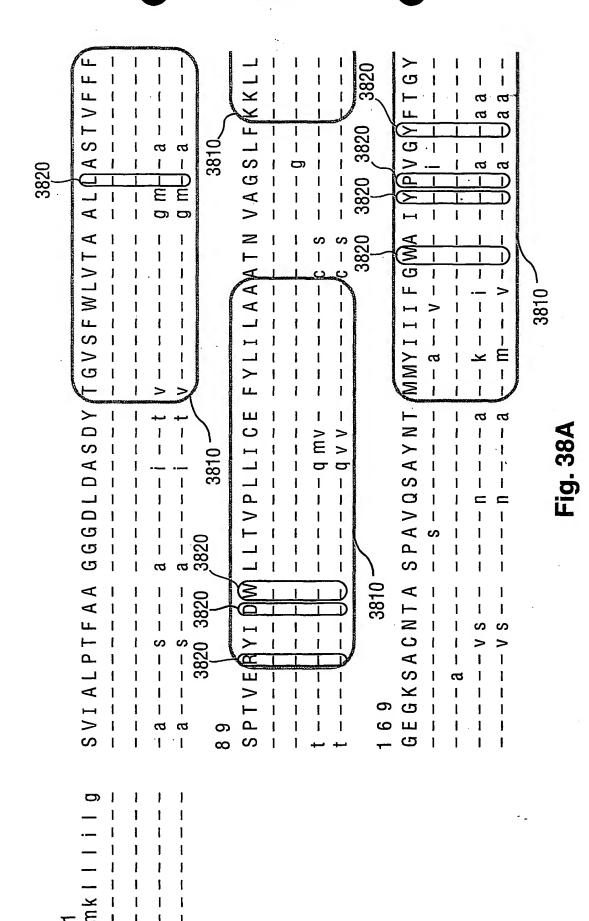
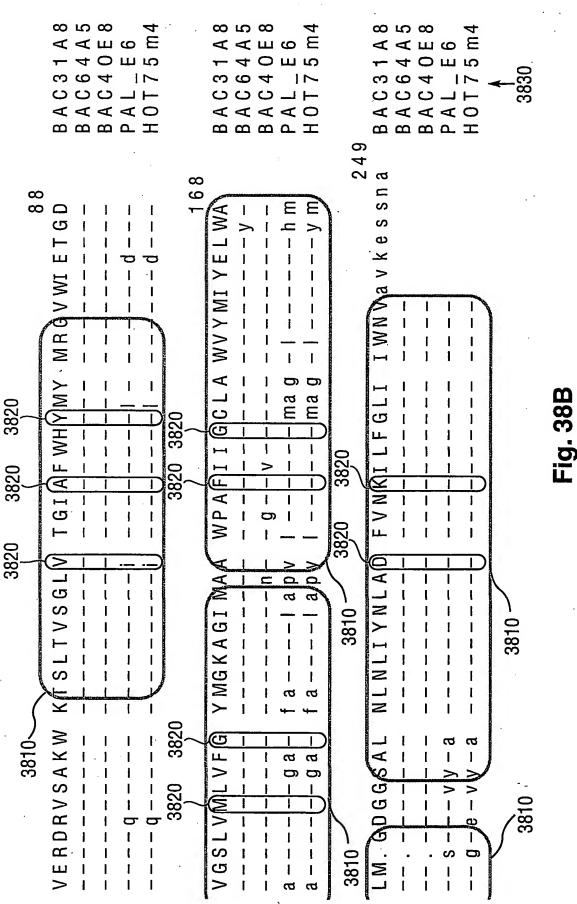


Fig. 37





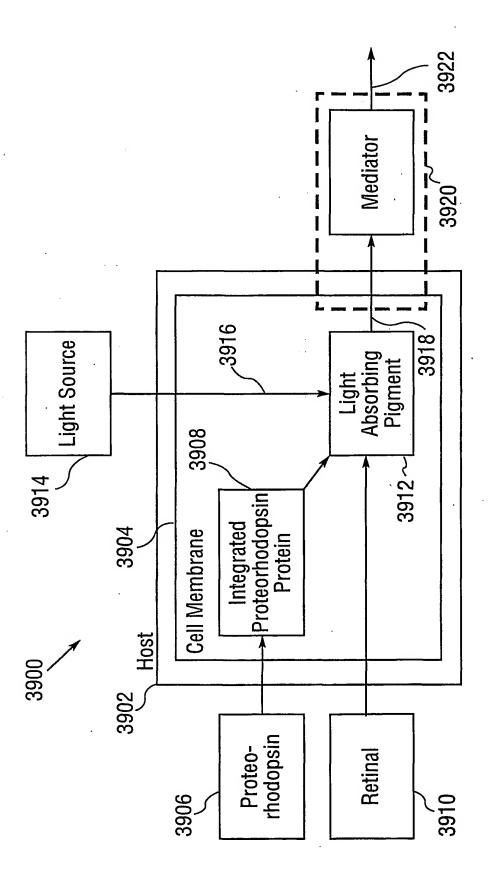
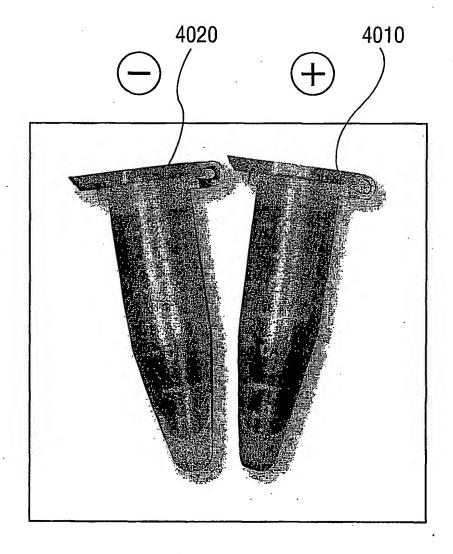


Fig. 39



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Fig. 40

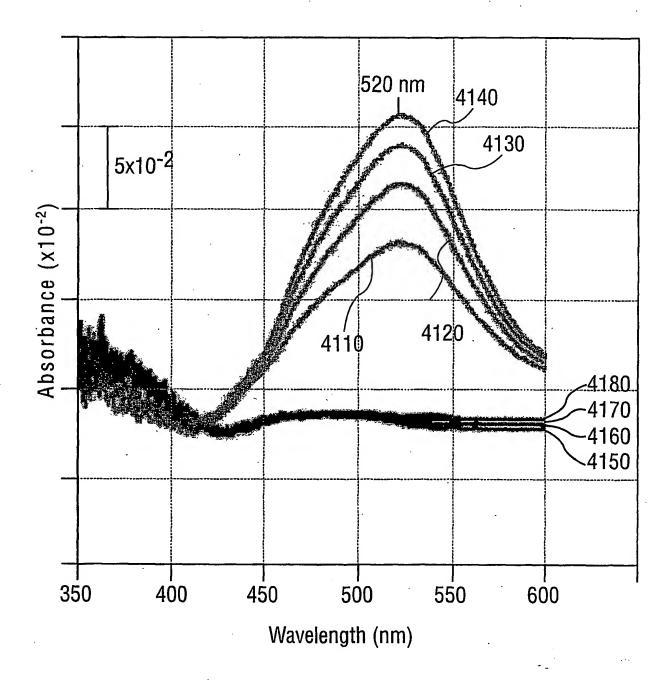


Fig. 41 BEST AVAILABLE COPY

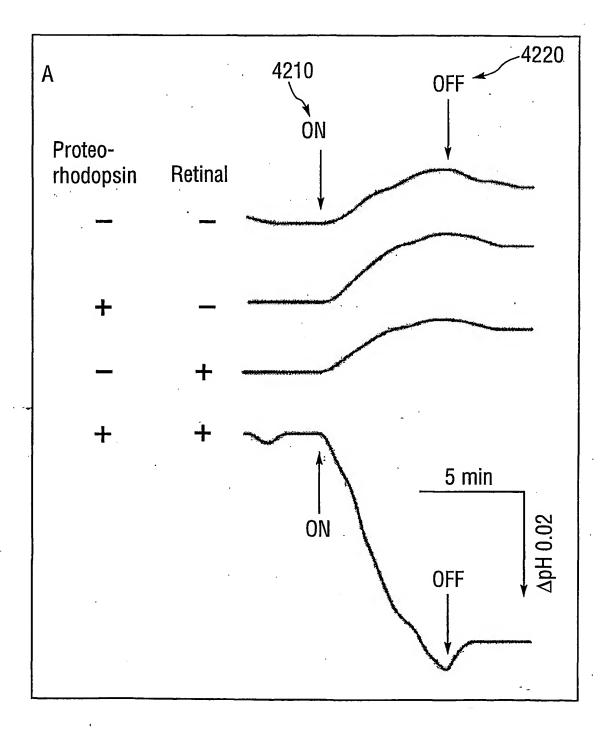


Fig. 42

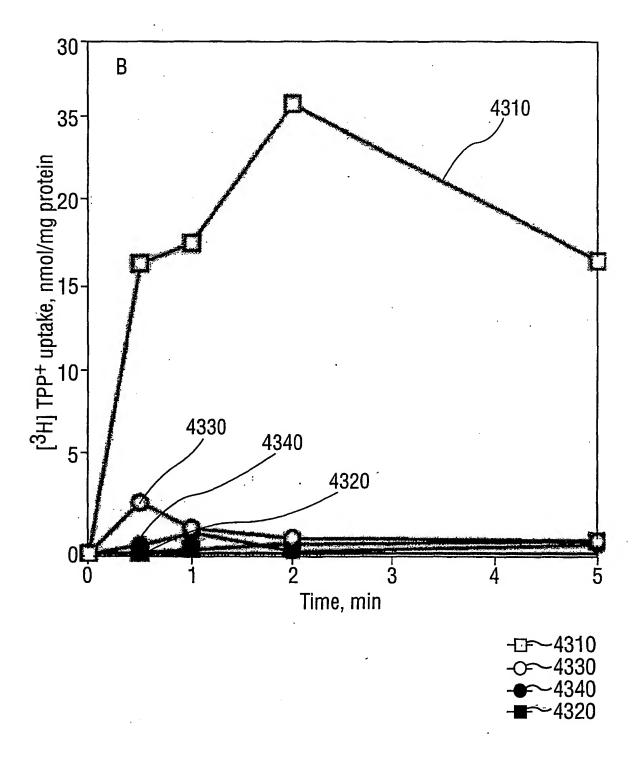


Fig. 43 BEST AVAILABLE COPY

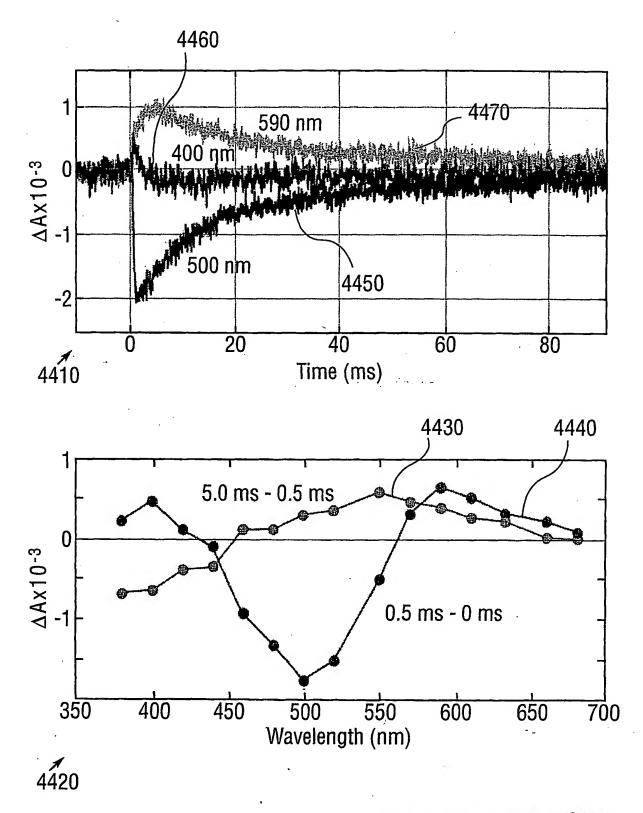
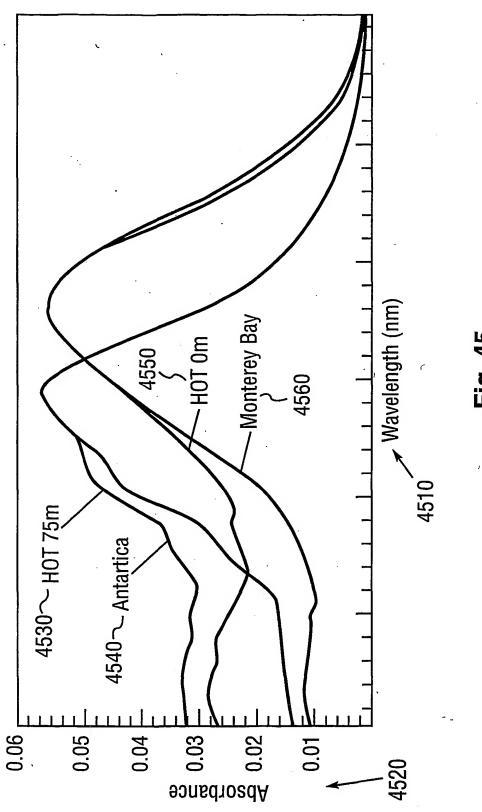


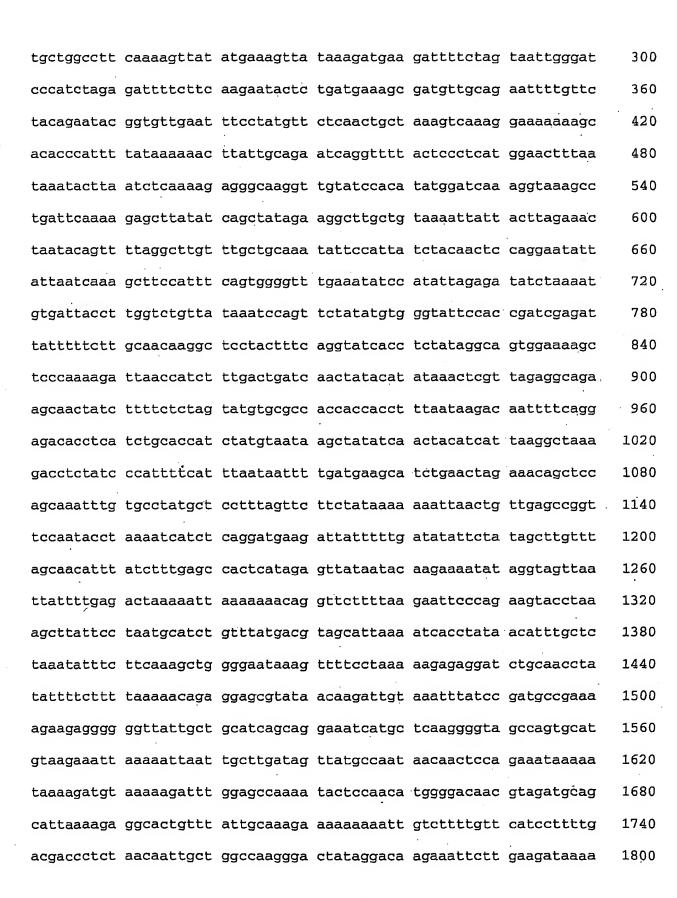
Fig. 44 BEST AVAILABLE COPY



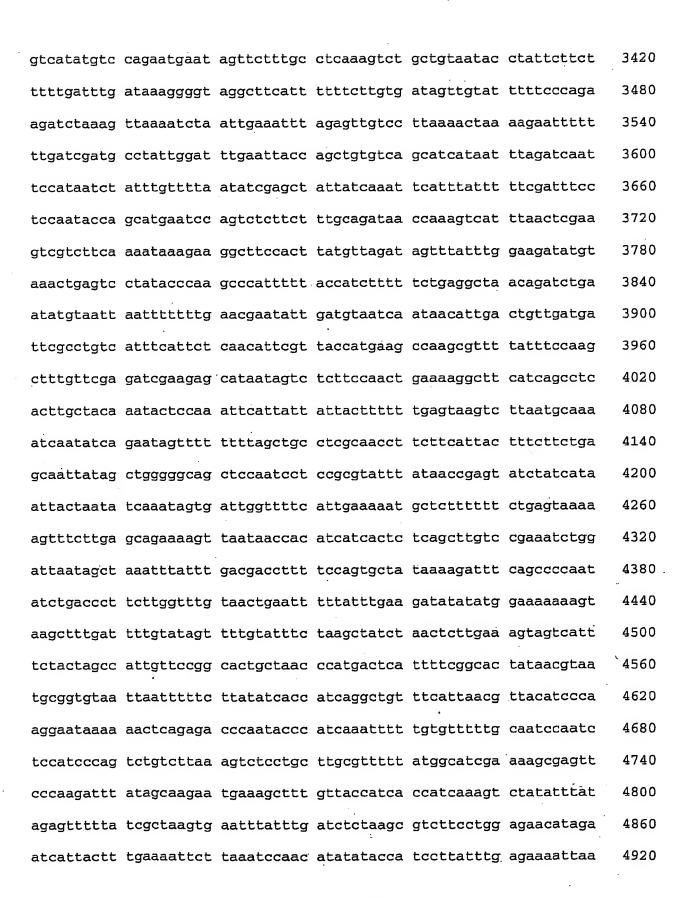
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<222>	CDS(complement) (50866)(51615) light-driven proton pump; has the properties of a light-driven oton pump when expressed with retinal in Escherichia col	pr
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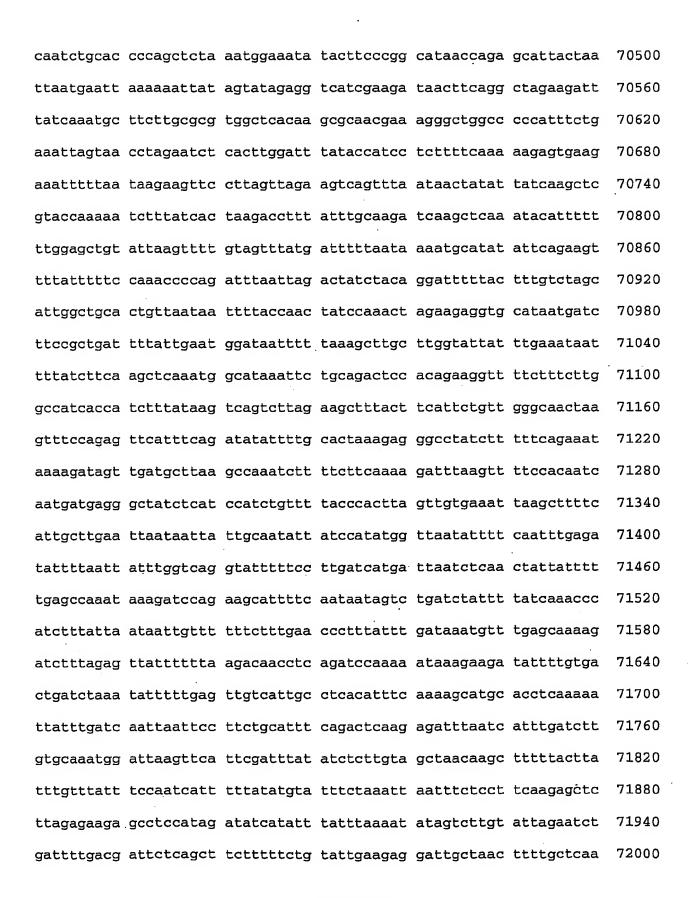






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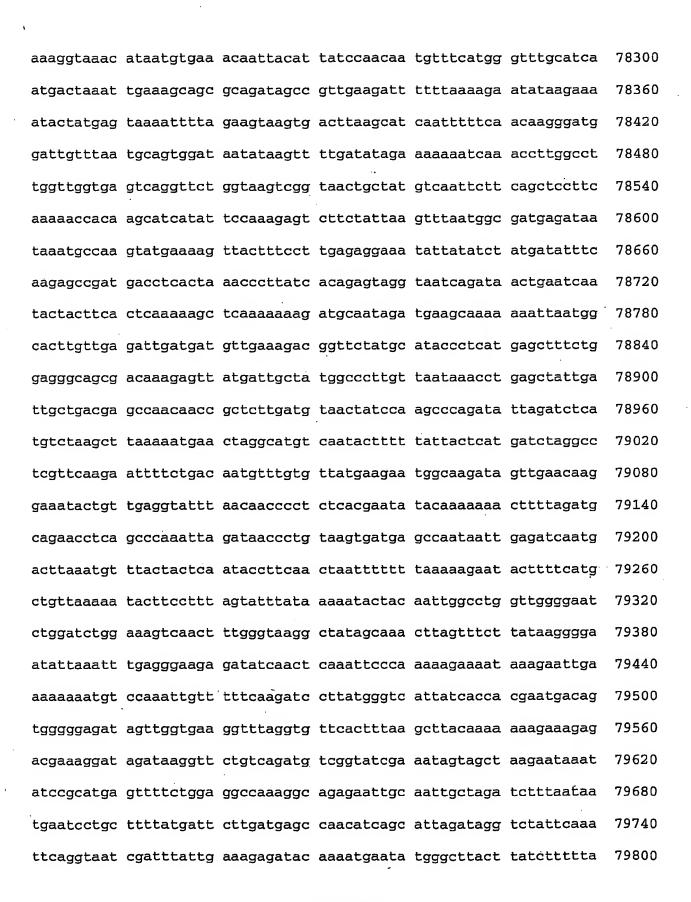












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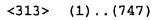
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Val Tyr Met Ile Tyr Glu Leu Trp Ala Gly Glu Gly Lys Ser Ala Cys-165 170 175

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288

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aga gga gta tgg att gaa act ggt gat tcg cct act gta ttt aga tac

Arg	G1y	Val	Trp	Ile 85	Glu	Thr	Gly	Asp	Ser 90	Pro	Thr	Val	Phe	Arg 95	Tyr	
					aca Thr						_	-				336
					act Thr											384
Leu					gtt Val											432
					tgg Trp 150											480
					gaa Glu											528
					tcg Ser				_				_	_		576
		_			tgg Trp											624
					ggt Gly											672
		_	_		gtt Val 230		_									720
					gaa Glu					٠		· .				750

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<211> 250

<212> PRT

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Tyr Leu Met Gly Asp Gly Gly Ser Ala Leu Asn Leu Asn Leu Ile Tyr

336

210 215 220

Asn Leu Ala Asp Phe Val Asn Lys Ile Leu Phe Gly Leu Ile Ile Trp 225 230 235 240

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<210> 14

<211> 750

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<220>

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<222> (1)..(750)

100

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								gat Asp				96
			_	_	_		_	tct Ser		_		144
								aaa Lys 60				192
								cat				240
								act Thr				288

att gat tgg tta cta aca gtt cct cta ttg ata tgt gaa ttc tac tta

Ile Asp Trp Leu Leu Thr Val Pro Leu Leu Ile Cys Glu Phe Tyr Leu

105

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				ctt Leu													432
				gct Ala													480
				tat Tyr 165													528
aat Asn	act Thr	gca Ala	agt Ser 180	cct Pro	gct Ala	gtg Val	caa Gln	tca Ser 185	gct Ala	tac Tyr	aac Asn	aca Thr	atg Met 190	atg Met	tat Tyr		576
				ggt Gly													624
Tyr				gac Asp													672
				ttt Phe												,	720
aat Asn					_				_							1	750
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Met Gly Lys Leu Leu Leu Ile Leu Gly Ser Val Ile Ala Leu Pro Thr 1 5 10 15

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Phe	Val 50	Glu	Arg	Asp	Arg	Val 55	Ser	Ala	Гуз	Trp	Lys 60	Thr	Ser	Leu	Thr
Val 65	Ser	Gly	Leu	Val	Thr 70	_	Ile	Ala	Phe	Trp 75	His	Tyr	Met	Tyr	Met 80
Arg	Gly	Val	Trp	Ile 85	Glu	Thr	Gly	Asp	Ser 90	Pro	Thr	Val	Phe	Arg 95	Tyr
Ile	Asp	Trp	Leu 100	Leu	Thr	Val	Pro	Leu 105	Leu	Ile	Суз	Glu	Phe 110	Tyr	Leu
Ile	Leu	Ala 115	Ala	Ala	Thr	Asn	Val 120	Ala	Ala	Gly	Leu	Phe. 125	Lys	Lys	Leu
Leu	Val 130	Gly	Ser	Leu	Val	Met 135	Leu	Val	Phe	Gly	Tyr 140	Met	Gly	Glu	Ala
Gly 145		Met	Asn	Ala	Trp 150	Gly	Ala	Phe	Val	Ile 155	Gly	Cys ·	Leu	Ala	Trp 160
Val	Tyr	Met	Ile	Туг 165	Glu	Lęu	Trp	Ala	Gly 170	Glu	Gly	Lys	Ala	Ala 175	Cys
Asn	Thr	Ala	Ser 180	Pro	Ala	Val	Gln	Ser 185	Ala	Tyr	Asn	Thr	Met 190	Met	Tyr
Ile	Ile	Ile 195	Phe	Gly	Trp	Ala	Ile 200	Tyr	Pro	Val	Gly	Tyr 205	Phe	Thr	Gly
Тут	Leu 210	Met	Gly	Asp	Gly	Gly 215	Ser	Ala	Ĺeu	Asn	Leu 220	Asn	Leu	Ile	Tyr
Asn 225	Leu	Ala	Asp	Phe	Val 230	Asn	·Lys	Ile	Leu	Phe 235	Gly	Leu	Ile	Ile	Trp 240

Asn Val Ala Val Lys Glu Ser Ser Asn Ala 245 250

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	aca gct ggt atg tta go Thr Ala Gly Met Leu Al 40		
	caa gtc agc gct aag to Gln Val Ser Ala Lys Tr 55		
Val Ser Gly Leu Ile T	act ggt ata gct ttt tg Thr Gly Ile Ala Phe Tr 70 75	p His Tyr Leu Tyr Met	
	gac act ggt gat acc co Asp Thr Gly Asp Thr Pr 90		
	act gtt cca tta caa at Thr Val Pro Leu Gln Me 105		
	aca agt gtt gct gct to Thr Ser Val Ala Ala Se 120		384
	gta atg tta ggt gct gg Val Met Leu Gly Ala Gl 135		432

	ta gct eu Ala															480
	ac atg Yr Met						. —		-		_	_	_	_		528
	ict gca Thr Ala							_			_			-	•	576
	itt gtt :le Val 195	Val			-				-			_	_			624
Tyr L	ta atg eu Met 10			_		-		_								672
	ac ctt sn Leu	-					-									720
	at gtt sn Val								Ala							753
											. •					
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Phe A	la Ala	Ala 20	Gly	Gly	Asp	Leu	Asp 25	Ile	Ser	Asp	Thr	Val 30	Gly	Val		
Ser P	he Trp 35	Leu	Val	Thr	Ala	Gly 40	Met	Leu	Ala	Ala	Thr 45	Val	Phe	Phe		
	al Glu	Arg	Asp	Gln	Val 55	Ser	Ala	ГЛЗ	Trp	Lys 60	Thr	Ser	Leu	Ala		

. 70 75. Arg Gly Val Trp Ile Asp Thr Gly Asp Thr Pro Thr Val Phe Arg Tyr 85 90 Ile Asp Trp Leu Leu Thr Val Pro Leu Gln Met Val Glu Phe Tyr Leu 100 105 Ile Leu Ala Ala Cys Thr Ser Val Ala Ala Ser Leu Phe Lys Lys Leu 115 120 125 Leu Ala Gly Ser Leu Val Met Leu Gly Ala Gly Phe Ala Gly Glu Ala Gly Leu Ala Pro Val Leu Pro Ala Phe Ile Ile Gly Met Ala Gly Trp 145 150 155 Leu Tyr Met Ile Tyr Glu Leu Tyr Met Gly Glu Gly Lys Ala Ala Val 165 170 175 Ser Thr Ala Ser Pro Ala Val Asn Ser Ala Tyr Asn Ala Met Met 180 185

Val Ser Gly Leu Ile Thr Gly Ile Ala Phe Trp His Tyr Leu Tyr Met

Ile Ile Val Val Gly Trp Ala Ile Tyr Pro Ala Gly Tyr Ala Ala Gly
195 200 205

Tyr Leu Met Gly Gly Glu Gly Val Tyr Ala Ser Asn Leu Asn Leu Ile 210 215 220

Tyr Asn Leu Ala Asp Leu Val Asn Lys Ile Leu Phe Gly Leu Ile Ile 225 230 235 240

Trp Asn Val Ala Val Lys Glu Ser Ser Asn Ala 245 250

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tca ttc tgg ctg gtt aca gct ggt atg tta gcg gca act gta ttc ttt  Ser Phe Trp Leu Val Thr Ala Gly Met Leu Ala Ala Thr Val Phe Phe  35  40  45										
ttt gta gaa aga gac caa gtc agc gct aag tgg aaa act tca ctt act 192 Phe Val Glu Arg Asp Gln Val Ser Ala Lys Trp Lys Thr Ser Leu Thr 50 55 60										
gta tct ggt tta att act ggt ata gct ttt tgg cat tat ctc tac atg Val Ser Gly Leu Ile Thr Gly Ile Ala Phe Trp His Tyr Leu Tyr Met 65 70 75 80										
aga ggt gtt tgg ata gat act ggt gat aca cca aca gta ttt aga tat 288 Arg Gly Val Trp Ile Asp Thr Gly Asp Thr Pro Thr Val Phe Arg Tyr 85 90 95										
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att ctt gct gct tgt aca agt gtt gct gct tca tta ttt aag aag ctt 384  Ile Leu Ala Ala Cys Thr Ser Val Ala Ala Ser Leu Phe Lys Lys Leu 115 120 125										
cta gct ggt tca tta gta atg tta ggt gct gga ttt gca ggc gaa gct Leu Ala Gly Ser Leu Val Met Leu Gly Ala Gly Phe Ala Gly Glu Ala 130 135 140										
ggt tta gct cct gta tta cct gct ttc att att ggt atg gct gga tgg Gly Leu Ala Pro Val Leu Pro Ala Phe Ile Ile Gly Met Ala Gly Tro 145 150 155 160										
tta tac atg att tat gag cta cat atg ggt gaa ggt aag gct gct gta 528 Leu Tyr Met Ile Tyr Glu Leu His Met Gly Glu Gly Lys Ala Ala Val										

																•	
				165	•				170					175			
_		_	_						_			gca Ala	-	Met	_		576
		_				_						tat Tyr 205	_	_			624
		Met			Asp				_		•	tta Leu					672
			-	_		_		_				ggt Gly	_		att Ile 240		720
		_		-	aaa Lys	_											753
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<213	3> I	Natu	cally	/ OCC	curri	ina d	ramma	a pro	oteol	aact e	ar i ur	n					
-101	25. •	10					,	•		Jack	<i></i>	••					•
<400 Met 1		19 Lys		•								Ala	Leu	Pro 15	Ser		•
Met 1	Gly	Lys ·	Leu	Leu 5	Leu	Ile	Leu	Gly	Ser 10	Ala	Ile			15			
Met 1 Phė	Gly	Lys	Leu Ala 20	Leu 5 Gly	Leu Gly	Ile Asp	Leu Leu	Gly Asp 25	Ser 10	Ala	Ile Asp	Ala	Val	15 Gly			
Met 1 Phė Ser	Gly Ala	Lys Ala Trp 35	Leu Ala 20 Leu	Leu 5 Gly Val	Leu Gly Thr	Ile Asp	Leu Leu Gly 40	Gly Asp 25	Ser 10 Ile Leu	Ala Ser Ala	Ile Asp Ala	Ala	Val 30 Val	15 Gly Phe	Val Phe		
Met 1 Phe Ser	Gly Ala Phe Val	Lys Ala Trp 35	Leu Ala 20 Leu Arg	Leu 5 Gly Val	Leu Gly Thr	Ile Asp Ala Val	Leu Leu Gly 40	Gly Asp 25 Met	Ser 10 Ile Leu	Ala Ser Ala	Ile Asp Ala Lys 60	Ala Thr Thr 45	Val 30 Val Ser	15 Gly Phe Leu	Val Phe Thr		

100 105 110 Ile Leu Ala Ala Cys Thr Ser Val Ala Ala Ser Leu Phe Lys Lys Leu 115 120 Leu Ala Gly Ser Leu Val Met Leu Gly Ala Gly Phe Ala Gly Glu Ala 135 Gly Leu Ala Pro Val Leu Pro Ala Phe Ile Ile Gly Met Ala Gly Trp 145 150 155 Leu Tyr Met Ile Tyr Glu Leu His Met Gly Glu Gly Lys Ala Ala Val 165 170 Ser Thr Ala Ser Pro Ala Val Asn Ser Ala Tyr Asn Ala Met Met Lys 180 Ile Ile Val Ile Gly Trp Ala Ile Tyr Pro Ala Gly Tyr Ala Ala Gly 195 200 205 Tyr Leu Met Ser Gly Asp Gly Val Tyr Ala Ser Asn Leu Asn Leu Ile 210 215 220 Tyr Asn Leu Ala Asp Phe Val Asn Lys Ile Leu Phe Gly Leu Ile Ile 225 230 235 Trp Asn Val Ala Val Lys Glu Ser Ser Asn Ala <210> 20 <211> 753 <212> DNA <213> Naturally occurring gamma proteobacterium <220> <221> CDS <222> (1)..(753)<223> Proteorhodopsin variant from pcr clone HOT75m4; GenBank #AF349981

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			gct Ala														96
	tca Ser	ttc Phe	tgg Trp 35	ctg Leu	gtt Val	aca Thr	gct Ala	ggt Gly 40	atg Met	tta Leu	gcg Ala	gca Ala	act Thr 45	gtg Val	ttc Phe	ttt Phe	144
	ttt Phe	gta Val 50	gaa Glu	aga Arg	gac Asp	caa Gln	gtc Val 55	agc Ser	gct Ala	aag Lys	tgg Trp	aaa Lys 60	act Thr	tca Ser	ctt Leu	act Thr	192
	gta Val 65	tct Ser	ggt Gly	tta Leu	att Ile	act Thr 70	ggt .Gly	ata Ile	gct Ala	ttt Phe	tgg Trp 75	cat His	tat Tyr	ctc Leu	tat Tyr	atg Met 80	240
,	aga Arg	ggt Gly	gtt Val	tgg Trp	ata Ile 85	gac Asp	act Thr	ggt Gly	gat Asp	acc Thr 90	cca Pro	aca Thr	gta Val	ttc Phe	aga Arg 95	tat Tyr	288
			tgg Trp												Tyr		336
	att Ile	ctt Leu	gct Ala 115	gct Ala	tgt Cys	aca Thr	agt Ser	gtt Val 120	gct Ala	gct Ala	tca Ser	tta Leu	ttt Phe 125	aag Lys	aag Lys	ctt Leu	384
	cta Leu	gct Ala 130	ggt Gly	tca Ser	tťa Leu	gta Val	atg Met 135	tta Leu	ggt Gly	gct Ala	gga Gly	ttt Phe 140	gca Ala	ggc Gly	gaa Glu	gct Ala	432
	gga Gly 145	tta Leu	gct Ala	cct Pro	gta Val	tta Leu 150	cct Pro	gct Ala	ttc Phe	att Ile	att Ile 155	ggt Gly	atg Met	gct Ala	gga Gly	tgg Trp 160	480
			atg Met														528
			gca Ala										Ala				576
	att Ile	att Ile	gtt Val	gtt Val	gga Gly	tgg Trp	gca Ala	att Ile	tat Tyr	cct Pro	gct Ala	gga Gly	tat Tyr	gct Ala	gct Ala	ggt Gly	624

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		aac aag att cta t Asn Lys Ile Leu P 235		
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Ser Phe Trp Leu 35		Gly Met Leu Ala A 40	la Thr Val Phe 45	Phe
Phe Val Glu Arg 50	Asp Gln Val ( 55	Ser Ala Lys Trp Ly 60		Thr
Val Ser Gly Leu 65	Ile Thr Gly :	Ile Ala Phe Trp H: 75	is Tyr Leu Tyr	Met 80
Arg Gly Val Trp	Ile Asp Thr (	Gly Asp Thr Pro Tl 90	hr Val Phe Arg 95	Tyr
Ile Asp Trp Leu 100		Pro Leu Gln Val Va 105	al Glu Phe Tyr 110	Leu
Ile Leu Ala Ala 115		Val Ala Ala Ser Le 120	eu Phe Lys Lys 125	Leu

Leu Ala Gly Ser Leu Val Met Leu Gly Ala Gly Phe Ala Gly Glu Ala 130 135 140 Gly Leu Ala Pro Val Leu Pro Ala Phe Ile Ile Gly Met Ala Gly Trp 145 150 155 160 Leu Tyr Met Ile Tyr Glu Leu Tyr Met Gly Glu Gly Lys Ala Ala Val 165 Ser Thr Ala Ser Pro Ala Val Asn Ser Ala Tyr Asn Ala Met Met 180 185 190 Ile Ile Val Val Gly Trp Ala Ile Tyr Pro Ala Gly Tyr Ala Ala Gly 195 200 Tyr Leu Met Gly Gly Glu Gly Val Tyr Ala Ser Asn Leu Asn Leu Ile 210 **215** · Tyr Asn Leu Ala Asp Phe Val Asn Lys Ile Leu Phe Gly Leu Ile Ile 225 230 235 Trp Asn Val Ala Val Lys Glu Ser Ser Asn Ala 245 <210> 22 <211> 753 <212> DNA <213> Naturally occurring gamma proteobacterium <220> <221> CDS <222> (1)..(753) <223> Proteorhodopsin variant from pcr clone HOT75m8: GenBank#AF349982 <400> 22 atg ggt aaa tta tta ctg ata tta ggt agt gct att gca ctt cca tca 48 Met Gly Lys Leu Leu Ile Leu Gly Ser Ala Ile Ala Leu Pro Ser 10 ttt gct gct gct ggt ggc gat cta gat ata agt gat act gtt ggt gtt 96

	Phe	Ala	Ala	Ala 20	Gly	Gly	Asp	Leu	Asp 25	Ile	Ser	Asp	Thr	Val 30	Gly	Val		
									atg Met									144
									gct Ala							act Thr		192
									gct Ala							atg Met 80		240
									gat Asp								:	288
									tta Leu 105						Tyr			336
									gct Ala								•	384
									ggt Gly									432
									ttc Phe									480
,									atg Met									528
									tct Ser 185	Ala								576
									tat Tyr									624
									tac Tyr									672
	tat	aac	ctt	gcc	gac	ctt	gtt	aac	aag	att	cta	ttt	ggt	ttg	atc	att		720

Tyr Asn Leu Ala Asp Leu Val Asn Lys Ile Leu Phe Gly Leu Ile Ile 230 235 240 tgg aat gtt gct gtt aaa gaa tct tct aat gct Trp Asn Val Ala Val Lys Glu Ser Ser Asn Ala 245 250 <210> 23 <211> 251 <212> PRT<213> Naturally occurring gamma proteobacterium <400> 23 Met Gly Lys Leu Leu Leu Gly Ser Ala Ile Ala Leu Pro Ser Phe Ala Ala Gly Gly Asp Leu Asp Ile Ser Asp Thr Val Gly Val 20 . 25 30 Ser Phe Trp Leu Val Thr Ala Gly Met Leu Ala Ala Thr Val Phe Phe 35 40 45 Phe Val Glu Arg Asp Gln Val Ser Ala Lys Trp Lys Thr Ser Leu Thr 50 60 Val Ser Gly Leu Ile Thr Gly Ile Ala Phe Trp His Tyr Leu Tyr Met 70 Arg Gly Val Trp Ile Asp Thr Gly Asp Thr Pro Thr Val Phe Arg Tyr 85 90 Ile Asp Trp Leu Leu Thr Val Pro Leu Gln Met Val Glu Phe Tyr Leu 100 105 110 Ile Leu Ala Ala Cys Thr Asn Val Ala Ala Ser Leu Phe Lys Lys Leu 115 120 Leu Ala Gly Ser Leu Val Met Leu Gly Ala Gly Phe Ala Gly Glu Ala 130 135 140 Gly Leu Ala Pro Val Trp Pro Ala Phe Ile Ile Gly Met Ala Gly Trp

145 150 155 160 Leu Tyr Met Ile Tyr Glu Leu Tyr Met Gly Glu Gly Lys Ala Ala Val 165 170 Ser Thr Ala Ser Pro Ala Val Asn Ser Ala Tyr Asn Ala Met Met Val 180 185 Ile Ile Val Val Gly Trp Ala Ile Tyr Pro Ala Gly Tyr Ala Ala Gly 200 195 205 Tyr Leu Met Gly Gly Glu Gly Val Tyr Ala Ser Asn Leu Asn Leu Ile 215 Tyr Asn Leu Ala Asp Leu Val Asn Lys Ile Leu Phe Gly Leu Ile Ile 230 235 Trp Asn Val Ala Val Lys Glu Ser Ser Asn Ala 245 250 <210> 24 <211> 750 <212> DNA <213> Naturally occurring gamma proteobacterium <220> <221> CDS <222> (1)..(750) <223> Proteorhodopsin variant from pcr clone MBOm1: GenBank#AF349983 <400> 24 atg ggt aaa tta tta ctg ata tta ggt agt gtt att gca ctt cct aca 48 Met Gly Lys Leu Leu Leu Gly Ser Val Ile Ala Leu Pro Thr ttt gct gca ggt ggt ggt gac ctt gat gct agt gat tac act ggt gtt 96 Phe Ala Ala Gly Gly Gly Asp Leu Asp Ala Ser Asp Tyr Thr Gly Val 20 25 tet ttt tgg tta gtt act get get eta tta gea tet act gta ttt tte 144 Ser Phe Trp Leu Val Thr Ala Ala Leu Leu Ala Ser Thr Val Phe Phe . 35 40 45 ttt gtt gaa aga gat aga gtt tct gca aaa tgg aaa aca tca tta act 192

## Phe Val Glu Arg Asp Arg Val Ser Ala Lys Trp Lys Thr Ser Leu Thr 50																		
Val Ser Gly Leu Val Thr Gly Ile Ala Phe Trp His Tyr Met Tyr Met 65  aga ggg gta tgg att gas act ggt gat tcg cca act gta ttt aga tac Arg Gly Val Trp Ile Glu Thr Gly Asp Ser Pro Thr Val Phe Arg Tyr 90  att gat tgg tta cta aca gtt cct cta ttg ata tgt gaa ttc tac tta Ile Asp Trp Leu Leu Thr Val Pro Leu Leu Ile Cys Glu Phe Tyr Leu 110  att ctt gct gct gca aca aat gtt gct gct ggc ctg ttt aag aaa tta Ile Leu Ala Ala Ala Thr Asn Val Ala Ala Gly Leu Phe Lys Lys Leu 115  ttg gtt ggt tct ctt gtt atg ctt gt gt gt ttt ggt tac atg ggt gag gca Leu Val Gly Ser Leu Val Met Leu Val Phe Gly Tyr Met Gly Glu Ala 130  gga att atg aca gct tgg cct gca ttc att att ggg tgt tta gct tgg Gly Ile Met Asn Ala Trp Pro Ala Phe Ile Ile Gly Cys Leu Ala Trp 145  gta tac atg att tat gaa cta tat gct gga gaa gga aaa tct gca tgt Val Tyr Met Ile Tyr Glu Leu Tyr Ala Gly Glu Gly Lys Ser Ala Cys 165  aat act gca agt cct tcg gtt ca tca tca gct tac aca aca aca atg atg gct Val Tyr Met Ile Tyr Glu Leu Tyr Ala Gly Glu Gly Lys Ser Ala Cys 165  aat act gca agt cct tcg gtt ca tca gct tac aca aca aca atg atg gct Asn Thr Ala Ser Pro Ser Val Gln Ser Ala Tyr Asn Thr Met Met Ala 180  atc ata gtc ttc ggt tgg gca att tat cct gta ggt tat ttc aca ggt 195  tac cta atg gt gac ggt gga tca gct ctt aca tac acc aca acc acc acc acc a	Phe		Glu	Arg	Asp	Arg		Ser	Ala	Lys	Trp		Thr	Ser	Leu	Thr		
Arg Gly Val Trp Ile Glu Thr Gly Asp Ser Pro Thr Val Phe Arg Tyr 95  att gat tgg tta cta aca gtt cct cta ttg ata tgt gaa ttc tac tta 110	Val					Thr					Trp					Met		240
The Asp Trp Leu Leu Thr Val Pro Leu Leu Ile Cys Glu Phe Tyr Leu 100 att ctt gct gct gca aca aat gtt gct gct gcc gcc ctg ttt aag aaa tta Ile Leu Ala Ala Ala Thr Asn Val Ala Ala Gly Leu Phe Lys Lys Leu 125 ttg gtt ggt tct ctt gtt atg ctt gtg ttt ggt ta atg ggt gag gca 432 Leu Val Gly Ser Leu Val Met Leu Val Phe Gly Tyr Met Gly Glu Ala 130 ser Leu Val Met Leu Val Phe Gly Tyr Met Gly Glu Ala 130 leu Cys Leu Ala Trp Pro Ala Phe Ile Ile Gly Cys Leu Ala Trp 155 l60 gta tac atg att tat gaa cta tat gct gga gaa aga aca tct gca tgt Val Tyr Met Ile Tyr Glu Leu Tyr Ala Gly Glu Gly Lys Ser Ala Cys 165 l75 aat act gca agt cct tcg gtt caa tca gct tac aac aca atg atg atg gct S76 Asn Thr Ala Ser Pro Ser Val Gln Ser Ala Tyr Asn Thr Met Met Ala 180 atc ata gct tcc ggt gga ca att tat cct gta ggt tat ttc aca ggt le Ile Val Phe Gly Trp Ala Ile Tyr Pro Val Gly Tyr Phe Thr Gly 200 cac ctt gct gct ctt aac acc act att acc cta atg ggt ga gga gga tca ctt tat tat cct gca tta tac acc ctt att tat Tyr Leu Met Gly Asp Gly Gly Ser Ala Leu Asn Leu Asn Leu Ile Tyr 215 acc ctt gct gct tac acc acc act att tat acc ctt gct gct gct gct gct gas cac gct tct acc cta gct tac acc ctt gct gct gct gct gct gas tca gct ctt acc acc ctt acc acc ctt att tat Gra gct leu Met Gly Asp Gly Gly Ser Ala Leu Asn Leu Asn Leu Ile Tyr 220 acc ctt gct gct gct acc acc acc acc acc acc acc acc acc a					Ile					Ser					Arg			288
The Leu Ala Ala Ala Thr Asn Val Ala Ala Gly Leu Phe Lys Lys Leu 115    ttg gtt ggt tct ctt gtt atg ctt gtg ttt ggt tac atg ggt gag gca   Leu Val Gly Ser Leu Val Met Leu Val Phe Gly Tyr Met Gly Glu Ala   130    gga att atg aac gct tgg cct gca ttc att att ggg tgt tta ggt tta ggt tta ggt tta ggt tta ggt tgg gg gga gca   Gly Ile Met Asn Ala Trp Pro Ala Phe Ile Ile Gly Cys Leu Ala Trp   160    gta tac atg att tat gaa cta tat gct gga gaa gga aaa tct gca tgt   Val Tyr Met Ile Tyr Glu Leu Tyr Ala Gly Glu Gly Lys Ser Ala Cys   175    aat act gca agt cct tcg gtt caa tca gct tac aac aca atg atg gct   Asn Thr Ala Ser Pro Ser Val Gln Ser Ala Tyr Asn Thr Met Met Ala   180    atc ata gtc ttc ggt tgg gca att tat cct gta ggt tat ttc aca ggt   185    atc ata gtc ttc ggt tgg gca att tat cct gta ggt tat ttc aca ggt   195    atc cta atg ggt gac ggt gga tca gct ctt aac tta acc ct aca ggt   196    tac cta atg ggt gac ggt gga tca gct ctt aac tta acc ctt att tat   190    ac cta atg ggt gac ggt gga tca gct ctt aac tta acc ctt att tat   190    tac cta atg ggt gac ggt gga tca gct ctt aac tta acc ctt att tat   190    ac cta atg ggt gac ggt gga tca gct ctt acc   185    185    185    185    186    186    187    188    188    188    189    189    189    189    189    189    189    189    189    189    189    189    189    189    189    189    189    189    189    189    189    189    189    189    189    189    189    189    189    189    189    189    189    189    189    189    189    189    189    189    189    189    189    189    189    189    189    189    189    189    189    189    189    189    189    189    189    189    189    189    189    189    189    189    189    189    189    189    189    189    189    189    189    189    189    189    189    189    189    189    189    189    189    189    189    189    189    189    189    189    189    189    189    189    189    189    189    189    189    189    189    189    189    189    189    189    189    189    189    189    189    189    189    189    189    189    189    189				Leu			_		Leu	_		_	_	Phe				336
gga att atg aac gct tgg cct gca ttc att att ggg tgg tta ggt tat gct tgg flu Ala Trp 150  gta tac atg att tat gaa cta tat gct gga gga gga agga a			Ala					Val					Phe					384
Gly Ile Met Asn Ala Trp 150		Val					Met					Tyr						432
Val Tyr Met Ile Tyr Glu Leu Tyr Ala Gly Glu Gly Lys Ser Ala Cys 175  aat act gca agt cct tcg gtt caa tca gct tac aac aca atg atg gct Ala Tyr Asn Thr Ala Ser Pro Ser Val Gln Ser Ala Tyr Asn Thr Met Met Ala 180  atc ata gtc ttc ggt tgg gca att tat cct gta ggt tat ttc aca ggt Ile Ile Val Phe Gly Trp Ala Ile Tyr Pro Val Gly Tyr Phe Thr Gly 200  tac cta atg ggt gac ggt gga tca gct ctt aac tta aac ctt att tat Tyr Leu Met Gly Asp Gly Gly Ser Ala Leu Asn Leu Asn Leu Ile Tyr 210  aac ctt gct gac ttt gtt aac aag att cta ttt ggt tta att ata tgg Asn Leu Ala Asp Phe Val Asn Lys Ile Leu Phe Gly Leu Ile Ile Trp 235  aat gtt gct gtt aaa gaa tct tct aat gct Asn Val Ala Val Lys Glu Ser Ser Asn Ala	Gly					Trp					Ile					Trp		480
Asn Thr Ala Ser Pro Ser Val Gln Ser Ala Tyr Asn Thr Met Met Ala 180 185 190  atc ata gtc ttc ggt tgg gca att tat cct gta ggt tat ttc aca ggt 624  Ile Ile Val Phe Gly Trp Ala Ile Tyr Pro Val Gly Tyr Phe Thr Gly 200 205  tac cta atg ggt gac ggt gga tca gct ctt aac tta aac ctt att tat 672  Tyr Leu Met Gly Asp Gly Gly Ser Ala Leu Asn Leu Asn Leu Ile Tyr 210 215 220  aac ctt gct gac ttt gtt aac aag att cta ttt ggt tta att ata tgg Asn Leu Ala Asp Phe Val Asn Lys Ile Leu Phe Gly Leu Ile Ile Trp 235 240  aat gtt gct gtt aaa gaa tct tct aat gct Asn Val Ala Val Lys Glu Ser Ser Asn Ala					Tyr					Gly					Ala			528
The The Val Phe Gly Trp Ala Ile Tyr Pro Val Gly Tyr Phe Thr Gly 200 205  tac cta atg ggt gac ggt gga tca gct ctt aac tta aac ctt att tat fyr Leu Met Gly Asp Gly Gly Ser Ala Leu Asn Leu Asn Leu Ile Tyr 210  aac ctt gct gac ttt gtt aac aag att cta ttt ggt tta att ata tgg 720  Asn Leu Ala Asp Phe Val Asn Lys Ile Leu Phe Gly Leu Ile Ile Trp 230  aat gtt gct gtt aaa gaa tct tct aat gct 750  Asn Val Ala Val Lys Glu Ser Ser Asn Ala				Ser					Ser					Met				576
Tyr Leu Met Gly Asp Gly Gly Ser Ala Leu Asn Leu Asn Leu Ile Tyr 210 215 220  aac ctt gct gac ttt gtt aac aag att cta ttt ggt tta att ata tgg 720 Asn Leu Ala Asp Phe Val Asn Lys Ile Leu Phe Gly Leu Ile Ile Trp 230 235 240  aat gtt gct gtt aaa gaa tct tct aat gct 750 Asn Val Ala Val Lys Glu Ser Ser Asn Ala			Val					Ile					Tyr				. *	62 <b>4</b>
Asn Leu Ala Asp Phe Val Asn Lys Ile Leu Phe Gly Leu Ile Ile Trp 225 230 235 240  aat gtt gct gtt aaa gaa tct tct aat gct Asn Val Ala Val Lys Glu Ser Ser Asn Ala		Leu					Gly					Leu						672
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		_			Lys	-				Ala	•	•						750

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Ser	Phe	Trp 35	Leu	Val	Thr	Ala	Ala 40	Leu	Leu	Ala	Ser	Thr 45	Val	Phe	Phe
Phe	Val 50	Glu	Arg	Asp	Arg	Val 55	Ser	Ala	Lys	Trp	Lys 60	Thr	Ser	Leu	Thr
Val 65	Şer	Gly	Leu	Val	Thr 70	Gly	Ile	Ala	Phe	Trp 75	His	Tyr	Met	Tyr	Met 80
Arg	Gly	Val	Trp	Ile 85	Glu	Thr	Gly	Asp	Ser 90	Pro	Thr	Val	Phe	Arg 95	Tyr
Ile	Asp	Trp	Leu 100	Leu	Thr	Val	Pro	Leu 105	Leu	Ile	Сув	Glu	Phe 110	Tyr	Leu
Ile	Leu	Ala 115	Ala	Ala	Thr	Asn	Val 120	Ala	Ala	Gly	Leu	Phe 125	Lys	Lys	Leu
Leu	Val 130	Gly	Ser	Leu	Val	Met 135	Leu	Val	Phe	Gly	Tyr 140		Gly	Gļu	Ala
Gly 145	Ile	Met	Asn	Ala	Trp 150	Pro	Ala	Phe	Ile	Ile 155	Gly	Cys	Leu	Ala	Trp 160
		-													

Asn Thr Ala Ser Pro Ser Val Gln Ser Ala Tyr Asn Thr Met Met Ala

Val Tyr Met Ile Tyr Glu Leu Tyr Ala Gly Glu Gly Lys Ser Ala Cys

.165

185 180 190 Ile Ile Val Phe Gly Trp Ala Ile Tyr Pro Val Gly Tyr Phe Thr Gly 195 200 Tyr Leu Met Gly Asp Gly Gly Ser Ala Leu Asn Leu Asn Leu Ile Tyr 210 215 220 Asn Leu Ala Asp Phe Val Asn Lys Ile Leu Phe Gly Leu Ile Ile Trp 225 230 235 Asn Val Ala Val Lys Glu Ser Ser Asn Ala 245 <210> 26 <211> 750 <212> DNA <213> Naturally ocurring gamma proteobacterium <220> <221> CDS <222> (1)..(750)<223> Proteorhodopsin variant from pcr clone MB0m2 <400> 26 atg ggt aaa tta tta ctg ata tta ggt agt gtt att gca ctt cct aca 48 Met Gly Lys Leu Leu Ile Leu Gly Ser Val Ile Ala Leu Pro Thr ttt get gea ggt ggt ggt gac ett gat get agt gat tae aet ggt gtt 96 Phe Ala Ala Gly Gly Gly Asp Leu Asp Ala Ser Asp Tyr Thr Gly Val 20 25 tet ttt tgg tta gtt act get get tta tta gea tet act gta ttt tte 144 Ser Phe Trp Leu Val Thr Ala Ala Leu Leu Ala Ser Thr Val Phe Phe ttt gtt gaa aga gat aga gtt tct gca aaa tgg aaa aca tca tta act 192 Phe Val Glu Arg Asp Arg Val Ser Ala Lys Trp Lys Thr Ser Leu Thr 50 55 60 gta tot ggt ott gtt act ggt att gct tto tgg cat tac atg tac atg-240 Val Ser Gly Leu Val Thr Gly Ile Ala Phe Trp His Tyr Met Tyr Met 65 70 75 80

aga ggg gta tgg att gaa act ggt gat tcg cca act gta ttt aga tac

Arg	Gly	Val	Trp	Ile 85	Glu	Thr	G1y		Ser 90	Pro	Thr	Val	Phe	Arg 95	Tyr		
															tta Leu		336
												ttt Phe 125			tta Leu		384
												atg Met				•	432
												tgt Cys				·	480
												aaa Lys					528
aat Asn	aca Thr	gca Ala	agt Ser 180	cct Pro	gct Ala	gtt Val	cag Gln	tca Ser 185	gct Ala	tac Tyr	aac Asn	aca Thr	atg Met 190	atg Met	atg Met		576
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<211> 250

<212> PRT

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<400> 27

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Ser Phe Trp Leu Val Thr Ala Ala Leu Leu Ala Ser Thr Val Phe Phe 35 40 45

Phe Val Glu Arg Asp Arg Val Ser Ala Lys Trp Lys Thr Ser Leu Thr 50 55 60

Val Ser Gly Leu Val Thr Gly Ile Ala Phe Trp His Tyr Met Tyr Met 65 70 75 80

Arg Gly Val Trp Ile Glu Thr Gly Asp Ser Pro Thr Val Phe Arg Tyr 85 90 95

Ile Asp Trp Leu Leu Thr Val Pro Leu Leu Ile Cys Glu Phe Tyr Leu 100 105 110

Ile Leu Ala Ala Ala Thr Asn Val Ala Ala Gly Leu Phe Lys Lys Leu 115 120 125

Leu Val Gly Ser Leu Val Met Leu Val Phe Gly Tyr Met Gly Glu Ala 130 135 140

Gly Ile Met Asn Ala Trp Gly Ala Phe Val Ile Gly Cys Leu Ala Trp 145 150 155 160

Val Tyr Met Ile Tyr Glu Leu Trp Leu Gly Glu Gly Lys Ala Ala Cys 165 170 175

Asn Thr Ala Ser Pro Ala Val Gln Ser Ala Tyr Asn Thr Met Met Met 180 185 190

Ile Ile Ile Phe Gly Trp Ala Ile Tyr Pro Val Gly Tyr Phe Thr Gly
195 200 205

Tyr Leu Met Gly Asp Gly Gly Ser Ala Leu Asn Leu Asn Leu Ile Tyr

210 215 . 220

Asn Leu Ala Asp Phe Val Asn Lys Ile Leu Phe Gly Leu Ile Ile Trp 225 230 235 240

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<223> Proteorhodopsin variant from pcr clone MB20m2; GenBank #AF349985

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Arg Gly Val Trp Ile Glu Thr Gly Asp Ser Pro Thr Val Phe Arg Tyr 85 90 95

att gat tgg tta cta aca gtt cct cta tta ata tgt gaa ttc tac tta 336

Ile Asp Trp Leu Leu Thr Val Pro Leu Leu Ile Cys Glu Phe Tyr Leu 100 105 110

aga ggg gta tgg att gaa act ggt gat tcg cca act gta ttt aga tac

	٠																
					gca Ala												384
					ctt Leu												432
					gct Ala											tgg Trp 160	480
					tat Tyr 165												528
					cct Pro												576
					ggt Gly											ggt Gly	624
			-		gac Asp				_								672
		Leu			ttt Phe												720
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	Ser	Phe	Trp 35	Leu	Val	Thr	Ala	Ala 40	Leu	Leu	Ala	Ser	Thr 45	Val	Phe	Phe
	Phe	Val 50	Glu	Arg	Asp	Arg	Val .55	Ser	Ala	Lys	Trp	<b>Lys</b> 60 	Thr	Ser	Leu	Thr
	Val 65	Ser	Gly	Leu	Val	Thr 70	Gly	Ile	Ala	Phe	Trp 75	His	Tyr	Met	Tyr	Met 80
	Arg	Gly	Val	Trp	Ile 85	Glu	Thr	Gly	Asp	Ser 90	Pro	Thr	Val	Phe	Arg 95	Tyr
	Ile	Asp	Trp	Leu 100	Leu	Thr	Val	Pro	Leu 105	Leu	Ile ·	Сув	Glu	Phe 110	Tyr	Leu
	Ile	Leu	Ala 115	Ala	Ala	Thr	Asn	Val 120	Ala	Ala	Gly	Leu	Phe 125	Lys	Lys	Leu
	Leu	Val 130	Gly	Ser	Leu	Val	Met 135	Leu	Val	Phe	Gly	Tyr 140	Met	Gly	Glu	Ala
	Gly 145	Ile	Met	Asn	Ala	Trp 150	Gly	Ala	Phe	Val	Ile 155	Gly	Суз	Leu	Ala	Trp 160
	Val	Tyr	Met	Île	Tyr 165	Glu	Leu	Trp	Ala	Gly 170	Glu	Gly	Lys	Ala	Ala 175	Cys
•	Asn	Thr	Ala	Ser 180	Pro	Ala	Val	Gln	Ser 185	Ala	Tyr	Asn	Thr	Met 190	Met	Tyr
	Ile	Ile	Ile 195	Phe	Gly	Trp	Ala	Ile 200	Tyr	Pro	Val	Gly	Tyr 205	Phe	Thr	Gly
,	Tyr	Leu 210	Met	Gly	Asp	Gly	Gly 215	Ser	Ala	Leu	Asn	Leu 220	Asn	Leu	Ile	Tyr
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		gca Ala														96
		tgg Trp 35														144
		gaa Glu														192
		ggt Gly														240
		gta Val														288
		tgg Trp												Tyr		336
		gct Ala 115														384
cta Leu	gtt Val 130	ggt Gly	tct Ser	ctt Leu	gtt Val	atg Met 135	ctt Leu	gtg Val	ttt Phe	ggt Gly	tac Tyr 140	atg Met	ggt Gly	gaa Glu	gca Ala	432

				gca Ala												480
				tat Tyr 165												528
				cct Pro									_	_	-	576
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				gac Asp				-								672
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Ser	Phe	Trp 35	Leu	Val	Thr	Ala	Ala 40	Leu	Leu	Ala	Ser	Thr 45	Val	Phe	Phe	
Phe	Val	Glu	Arg	Asp	Arg	Val 55	Ser	Ala	Lys	Trp	Lys 60	Thr	Ser	Leu	Thr	

Val Ser Gly Leu Val Thr Gly Ile Ala Phe Trp His Tyr Met Tyr Met 75 Arg Gly Val Trp Ile Glu Thr Gly Asp Ser Pro Thr Val Phe Arg Tyr 85 90 Ile Asp Trp Leu Leu Thr Val Pro Leu Leu Ile Cys Glu Phe Tyr Leu Ile Leu Ala Ala Ala Thr Asn Val Ala Gly Ser Leu Phe Lys Lys Leu 120 Leu Val Gly Ser Leu Val Met Leu Val Phe Gly Tyr Met Gly Glu Ala 135 Gln Ile Met Ala Ala Trp Pro Ala Phe Ile Ile Gly Cys Leu Ala Trp 145 150 155 Val Tyr Met Ile Tyr Glu Leu Tyr Ala Gly Glu Gly Lys Ser Ala Cys 165 170 Asn Thr Ala Ser Pro Ser Val Gln Ser Ala Tyr Asn Thr Met Met Ala 180 185 190 Ile Ile Val Phe Gly Trp Ala Ile Tyr Pro Val Gly Tyr Phe Thr Gly 195 200 205 Tyr Leu Met Gly Asp Gly Gly Ser Ala Leu Asn Leu Asn Leu Ile Tyr 210 215 Asn Leu Ala Asp Phe Val Asn Lys Ile Leu Leu Gly Leu Ile Ile Trp 230 235

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<211> 750

<212> DNA

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		gca Ala															96
		tgg Trp 35															144
	_	gaa Glu	_	_	_	_		_									192
_		ggt Gly		_				_					_		_	·	240
		gta Val			_		. — —	_	_			_		_			288
	-	tgg Trp				_					_	_				•	336
		gct Ala 115	-				_	_					_				384
Leu		ggt Gly															432
		atg Met															480
		atg Met														!	528

		Ala	_		_	-			-		aac Asn		_	_		576
						-		$\mathtt{Tyr}$			ggt Gly					624
	_				. –			_			tta Leu 220					672
											ggt Gly					720
	_			aaa Lys 245	-				_							750
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Phe	Ala	А1а	<b>61.</b>									-				
		1110	20 20	GIY	GIA	Asp	Leu	Asp 25	Ala	Ser	Asp	Tyr	Thr 30	Gly	Val	*, *
Ser			20					25	÷.		Asp Ser		30			
	Phe	Trp 35	20 Leu	Val	Thr	Ala	Ala 40	25 Leu	Leu	Ala		Thr 45	30 Val	Phe	Phe	
Phe	Phe Val 50	Trp 35 Glu	20 Leu Arg	Val Asp	Thr Arg	Ala Val 55	Ala 40 Ser	25 Leu Ala	Leu Lys Phe	Ala Trp	Ser	Thr 45 Thr	30 Val Ser	Phe Leu	Phe Thr	

Arg Gly Val Trp Ile Glu Thr Gly Asp Ser Pro Thr Val Phe Arg Tyr 85 90 95

Ile Asp Trp Leu Leu Thr Val Pro Leu Leu Ile Cys Glu Phe Tyr Leu 105

Ile Leu Ala Ala Ala Ala Asn Val Ala Gly Ser Leu Phe Lys Lys Leu 115

Leu Val Gly Ser Leu Val Met 135

Cly Ile Met Ala Ala Trp Pro Ala Phe Ile Ile Gly Cys Leu Ala Trp 145

Val Tyr Met Ile Tyr Glu Leu Trp Ala Gly Glu Gly Lys Ser Ala Cys 175

Asn Thr Ala Ser Pro Ala Val Gln Ser Ala Tyr Asn Thr Met Met Tyr 180 185 190

Ile Ile Ile Phe Gly Trp Ala Ile Tyr Pro Val Gly Tyr Phe Thr Gly
195 200 205

Tyr Leu Met Gly Asp Gly Gly Ser Ala Leu Asn Leu Asn Leu Ile Tyr 210 215 220

Asn Leu Ala Asp Phe Val Asn Lys Ile Leu Phe Gly Leu Ile Ile Trp 225 230 235 240

Asn Val Ala Val Lys Glu Ser Ser Asn Ala 245 250

<210> 34

<211> 750

<212> DNA

<213> Naturally occurring gamma proteobacterium

<220>

<221> CDS

<222> (1)..(750)

<223> Proteorhodopsin variant from pcr clone MB40m1; GenBank #AF349988

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			aga Arg									192
			act Thr 70									240
			gaa Glu									288
-			aca Thr	-				_	_			336
	 	_	act Thr		_	-				_		384
			gtt Val									432
			tgg Trp 150									480
			gaa Glu									528
			gct Ala									576
	Phe		tgg Trp									624

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Ser	Phe	Trp 35	Leu	Val	Thr	Ala	Ala 40	Leu	Leu	Ala	Ser	Thr 45	Val	Phe	Phe	,
Phe	Val 50	Glu	Arg	Asp	Arg	Val 55	Ser	Ala	Lys	Trp	Lys 60	Thr	Ser	Leu	Thr	
Val 65	Ser	Gly	Leu	Val	Thr 70	Gly	Ile	Ala	Phe	Trp 75		Tyr	Met	Tyr	Met 80	
Arg	Gly	Val	Trp	Ile 85	Glu	Thr	Gly	Asp	Ser 90	Pro	Thr	Val	Phe	Arg 95	Tyr	
Ile	Asp	Trp	Leu 100	Leu	Thr	Val	Pro	Leu 105	Leu	Ile	Cys	Glu	Phe 110	Tyr	Leu	
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Leu	Val 130	Gly	Ser	Leu	Val	Met 135	Leu	Val	Phe	Gly	Tyr 140	Met	Gly	Glu	Ala		
Gly 145	Ile	Met	Ala	Ala	Trp 150	Pro	Ala	Phe	Ile	155	Gly	Сув	Ļeu	Ala	Trp 160		
Val	Tyr	Met	Ile	туr 165	Glu	Leu	Tyr	Ala	Gly 170	Glu	Gly	Lys	Ser	Ala 175	Cys		
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Ile	Ile	Val 195	Phe	Gly	Trp	Ala	Ile 200	Tyr	Pro	Val	Gly	Tyr 205		Thr	Gly		
Tyr	Leu 210	Met	Gly	Asp	Gly	Gly 215	Ser	Ala	Leu	Asn	Leu 220	Asn	Leu	Ile	Tyr	•	
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atg		aaa							Ser		att Ile			Pro			48
											gat Asp						96

			•														
				_		-	-			_		act Thr 45	_				144
												aca Thr				-	192
												tac Tyr					240
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												gaa Glu					336
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	Ile											tgt Cys					480
												aag Lys					528
												aca Thr		-			576
												tat Tyr 205					624
												aac Asn					672
aac Asn 225	ctt Leu	gct Ala	gac Asp	ttt Phe	gtt Val 230	aac Asn	aag Lys	aat Asn	cta Leu	ttt Phe 235	ggt Gly	tta Leu	att Ile	ata Ile	tgg Trp 240		720

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Val	Tyr	Met	Ile	Туг 165	Glu	Leu	Trp	Ala	Gly 170	Ģlu	Gly	Lys	Ala	Ala 175	Cys	
Asn	Thr	Ala	Ser 180	Pro	Ala	Val	G1n	Ser 185	Ala	Tyr	Asn	Thr	Met 190	Met	Tyr	
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											gat Asp	Tyr				96
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	50					5,5					60						
_				gtt Val													240
_		_		att Ile 85	-				-								288
	_			cta Leu		_					_	_					336
		-	_	gca Ala			_	_									384
	-			ctt Leu												,	432
				gca Ala													480
				tat Tyr 165													528
		_	_	cct Pro	_				_								576
Ile	Ile	Ile 195	Val	ggt Gly	Trp	Ala	Ile 200	Tyr	Pro	Val	Gly	Tyr 205	Phe	Thr	Gly		624
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Phe Val Glu Arg Asp Arg Val Ser Ala Lys Trp Lys Thr Ser Leu Thr 50 55 60

Val Ser Gly Leu Val Thr Gly Ile Ala Phe Trp His Tyr Met Tyr Met 65 70 75 80

Arg Gly Val Trp Ile Glu Thr Gly Asp Ser Pro Thr Val Phe Arg Tyr 85 90 95

Ile Asp Trp Leu Leu Thr Val Pro Leu Leu Ile Cys Glu Phe Tyr Leu
100 105 ...110

Ile Leu Ala Ala Ala Thr Asn Val Ala Gly Ser Leu Phe Lys Lys Leu 115 120 125

Leu Val Gly Ser Leu Val Met Leu Val Phe Gly Tyr Met Gly Glu Ala 130 135 140

Gly Ile Met Ala Ala Trp Pro Ala Phe Ile Ile Gly Cys Leu Ala Trp 145 150 155 160

Val Tyr Met Ile Tyr Glu Leu Trp Ala Gly Glu Gly Lys Ser Ala Cys 165 170 175

Asn Thr Ala Ser Pro Ala Val Gln Ser Ala Tyr Asn Thr Met Met Tyr 180 185 190

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	Asn 225	Leu	Ala	Asp	Phe	Val 230	Asn	Lys	Ile	Leu	Phe <sup>2</sup>	Gly	Leu	Ile	Ile	Trp 240	
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		Phe										tct Ser					144
		_	_	_	_	_	_		_			aaa Lys 60				act Thr	192
•	_				_				_			cat His		_			240
	· ·													•			

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•			•
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		tc att att ggg tgt he Ile Ile Gly Cys 155	
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_	Pro Ser Val Gln S	ca gct tac aac aca er Ala Tyr Asn Thr 85	
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Ser Phe Trp Leu Val Thr Ala Ala Leu Leu Ala Ser Thr Val Phe Phe 35 40 45

Phe Val Glu Arg Asp Arg Val Ser Ala Lys Trp Lys Thr Ser Leu Thr 50 55 60

Val Ser Gly Leu Val Thr Gly Ile Ala Phe Trp His Tyr Met Tyr Met 65 70 75 80

Arg Gly Val Trp Ile Glu Thr Gly Asp Ser Pro Thr Val Phe Arg Tyr 85 90 95

Ile Asp Trp Leu Leu Thr Val Pro Leu Leu Ile Cys Glu Phe Tyr Leu
100 105 110

Ile Leu Ala Ala Ala Thr Asn Val Ala Gly Ser Leu Phe Lys Lys Leu 115 120 125

Leu Val Gly Ser Leu Val Met Leu Val Phe Gly Tyr Met Gly Glu Ala 130 135 140

Gly Ile Met Ala Ala Trp Pro Ala Phe Ile Ile Gly Cys Leu Ala Trp 145 150 155 160

Val Tyr Met Ile Tyr Glu Leu Tyr Ala Gly Glu Gly Lys Ser Ala Cys 165 170 175

Asn Thr Ala Ser Pro Ser Val Gln Ser Ala Tyr Asn Thr Met Met Ala .180 185 190

Ile Ile Val Phe Gly Trp Ala Ile Tyr Pro Val Gly Tyr Phe Thr Gly
195 200 205

Tyr Leu Met Gly Asp Gly Gly Ser Ala Leu Asn Leu Asn Leu Ile Tyr 210 215 220

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gta tct ggt ctt gtt act ggt att gct ttc tgg cat tac atg tac atg Val Ser Gly Leu Val Thr Gly Ile Ala Phe Trp His Tyr Met Tyr Met 65 70 75 80
aga ggg gta tgg att gaa act ggt gat tcg cca act gta ttt aga tac 288 Arg Gly Val Trp Ile Glu Thr Gly Asp Ser Pro Thr Val Phe Arg Tyr 85 90 95
att gat tgg tta cta aca gtt cct cta tta ata tgt gaa ttc tac tta 336  Ile Asp Trp Leu Leu Thr Val Pro Leu Leu Ile Cys Glu Phe Tyr Leu- 100 105 110
att ctt gct gct gct act aat gtt gcc ggc tca tta ttt aag aaa ctt 384 Ile Leu Ala Ala Ala Thr Asn Val Ala Gly Ser Leu Phe Lys Lys Leu

115	12	20	125	
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		ca ttc att att ggg la Phe Ile Ile Gl 155		
		at gct gga gaa gg yr Ala Gly Glu Gl 170		
		aa tca gct tac aa ln Ser Ala Tyr As 185		
	Gly Trp Ala Il	tt tat cct gta gg le Tyr Pro Val Gl 00		
		ca gct ctt aac tt er Ala Leu Asn Le 22	u Asn Leu Ile	
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Ser Phe Trp Leu 35	Val Thr Ala Al	la Leu Leu Ala Se: O	r Thr Val Phe 45	Phe

Phe Val Glu Arg Asp Arg Val Ser Ala Lys Trp Lys Thr Ser Leu Thr 50 55 60

Val Ser Gly Leu Val Thr Gly Ile Ala Phe Trp His Tyr Met Tyr Met 65 70 75 80

Arg Gly Val Trp Ile Glu Thr Gly Asp Ser Pro Thr Val Phe Arg Tyr 85 90 95

Ile Asp Trp Leu Leu Thr Val Pro Leu Leu Ile Cys Glu Phe Tyr Leu 100 105 110

Ile Leu Ala Ala Ala Thr Asn Val Ala Gly Ser Leu Phe Lys Lys Leu 115 120 125

Leu Val Gly Ser Leu Val Met Leu Val Phe Gly Tyr Met Gly Glu Ala 130 135 140

Gly Ile Met Ala Ala Trp Pro Ala Phe Ile Ile Gly Cys Leu Ala Trp 145 150 155 160

Val Tyr Met Ile Tyr Glu Leu Tyr Ala Gly Glu Gly Lys Ser Ala Cys 165 170 175

Asn Thr Ala Ser Pro Ser Val Gln Ser Ala Tyr Asn Thr Met Met Ala 180 185 190

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195 200 205

Tyr Leu Met Gly Asp Gly Gly Ser Ala Leu Asn Leu Asn Leu Ile Tyr 210 215 220

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Asn Ala Ala Val Lys Glu Ser Ser Asn Ala 245 250

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												tac Tyr				2	240
												gta Val				2	888
												gaa Glu				3	336
			Ala									ttt Phe 125				3	884
												atg Met				. 4	132
												tgt Cys				4	180

	145					150					155			`		160		
												gga Gly						528
												.aac Asn		_	_		٠	576
						_					_	ggt Gly				ggt Gly		624
•												tta Leu 220						672
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	Ser	Phe	Trp 35	Leu	Val	Thr	Ala	Ala 40	Leu	Leu	Ala	Ser	Thr 45	Val	Phe	Phe		
	Phe	Val 50	Glu	Arg	Asp	Arg	Val 55	Ser	Ala	Lys	Trp	Lys 60	Thr	Ser	Leu	Thr		
	Val 65	Ser	Gly	Leu	Val	Thr 70	Gly	Ile	Ala	Phe	Trp 75	His	Tyr	Met	Tyr	Met 80		

WO 01/83701 PCT/US01/14394

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Ile Asp Trp Leu Leu Thr Val Pro Leu Leu Ile Cys Glu Phe Tyr Leu 100 105 110

Ile Leu Ala Ala Ala Thr Asn Val Ala Gly Ser Leu Phe Lys Lys Leu 115 120 125

Leu Val Gly Ser Leu Val Met Leu Val Phe Gly Tyr Met Gly Glu Ala 130 135 140

Gly Ile Met Ala Ala Trp Pro Ala Phe Ile Ile Gly Cys Leu Ala Trp 145 150 155 160

Val Tyr Met Ile Tyr Glu Leu Trp Ala Gly Glu Gly Lys Ser Ala Cys 165 170 175

Asn Thr Ala Ser Pro Ala Val Gln Ser Ala Tyr Asn Thr Met Met Tyr 180 185 190

Ile Ile Ile Phe Gly Trp Ala Ile Tyr Pro Val Gly Tyr Phe Thr Gly 195 200 205

Tyr Leu Met Gly Asp Gly Gly Ser Ala Leu Asn Leu Asn Leu Ile Tyr 210 215 220

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att ctt gct gct Ile Leu Ala Ala 115		1 Ala Gly Se		
cta gtt ggt tct Leu Val Gly Ser 130				
gga ata atg gcg Gly Ile Met Ala 145			al Gly Cys Leu	
gta tat`atg att Val Tyr Met Ile				
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			_		_							cta Leu 220					672
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		_	_	_		-			aat Asn							٠	750
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]	Phe	Ala	Ala	Gly 20	Gly	Gly	Asp	Leu	Asp 25	Ala	Ser	Asp	Tyr	Thr 30	Gly	Val	
9	Ser	Phe	Trp	Leu	Val	Thr	Ala	Ala 40	Leu	Leu	Ala	Ser	Thr 45	Val	Phe	Phe	
			33												•		
	Phe	Val 50		Arg	Asp	Arg	Val 55		Ala	Lys	Trp	Lys 60	Thr	Ser	Leu	Thr	
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Ile Asp Trp Leu Leu Thr Val Pro Leu Leu Ile Cys Glu Phe Tyr Leu

Arg Gly Val Trp Ile Glu Thr Gly Asp Ser Pro Thr Val Phe Arg Tyr-

100 105 110

Ile Leu Ala Ala Ala Thr Asn Val Ala Gly Ser Leu Phe Lys Lys Leu 115 120 125

Leu Val Gly Ser Leu Val Met Leu Val Phe Gly Tyr Met Gly Glu Ala 130 135 140

Gly Ile Met Ala Ala Trp Pro Ala Phe Ile Val Gly Cys Leu Ala Trp 145 150 155 160

Val Tyr Met Ile Tyr Glu Leu Trp Ala Gly Glu Gly Lys Ser Ala Cys 165 170 175

Asn Thr Ala Ser Pro Ala Val Gln Ser Ala Tyr Asn Thr Met Met Tyr 180 185 190

Ile Ile Ile Val Gly Trp Ala Ile Tyr Pro Val Gly Tyr Phe Thr Gly
195 200 205

Tyr Leu Met Gly Asp Gly Gly Ser Ala Leu Asn Leu Asn Leu Ile Tyr 210 215 220

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WO 01/83701

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								atg Met								1	.44
								gct Ala								1	.92
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								gat Asp								2	. 88
								tta Leu 105									336
								gct Ala								3	884
								ggt Gly									132
								ttc Phe								4	180
								atg Met								5	528
								tct Ser 185								5	576
								tat Tyr							ggt- Gly	6	524
tac	cta	atg	agt	ggt	gac	ggt	gta	tac	gct	tca	aac	tta	aac	ctt	ata	6	72

720

753

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Ser	Phe	Trp 35	Leu	Val	Thr	Ala	Gly 40	Met	Leu	Ala	Ala	Thr 45	Val	Phe	Phe	
Phe	Val 50	Glu	Arg	Asp	Gln	Val 55	Ser	Ala	Lys	Trp	Lys 60	Thr	Ser	Leu	Thr	
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Arg	Gly	Val	Trp	Ile 85	Asp	Thr	Gly	Asp	Thr 90	Pro	Thr	Val	Phe	Arg 95	Tyr	
Ile	Asp	Trp	Leu 100	Leu	Thr	Val	Pro	Leu 105	Gln	Met	Val	Glu	Phe 110	Tyr	Leu	
Ile	Leu	Ala 115	Aļa	Cys	Thr	Ser	Val 120	Ala	Ala	Ser	Leu	Phe 125	Lys	Lys	Leú⁻	

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Ser Thr Ala Ser Pro Ala 180	Val Asn Ser Ala Tyr 185	Asn Ala Met Met Lys 190
Ile Ile Val Ile Gly Trp 195	Ala Ile Tyr Pro Ala 200	Gly Tyr Ala Ala Gly 205
Tyr Leu Met Ser Gly Asp 210	Gly Val Tyr Ala Ser 215	Asn Leu Asn Leu Ile 220
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Trp Asn Val Ala Val Lys 245	Glu Ser Ser Asn Ala . 250	
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ttt gct gct gct ggt ggc Phe Ala Ala Ala Gly Gly 20		

144

tca ttc tgg ctg gtt aca gct ggt atg tta gcg gca act gtg ttc ttt

							•										
Ser	Phe	Trp 35	Leu	Val	Thr	Ala	Gly 40	Met	Leu	Ala	Ala	Thr 45	Val	Phe	Phe	-	
										tgg Trp							192
										tgg Trp 75							240
										cca Pro							288
										atg Met							336
										tca Ser							384
							Leu			gga Gly							432
										att Ile 155							480
										gaa Glu							528
										tac Tyr							576
										gct Ala						· ·	624
										tca Ser		Leu					672
										cta Leu 235							720
tgg	aat	gtt	gct	gtt	aaa	gaa	tct	tct	aat	gct							753

Trp Asn Val Ala Val Lys Glu Ser Ser Asn Ala 245 250

<210> 51

<211> 251

<212> PRT

<213> Naturally occurring gamma proteobacterium

<400> 51

Met Gly Lys Leu Leu Leu Ile Leu Gly Ser Ala Ile Ala Leu Pro Ser 1 5 10 15

Phe Ala Ala Gly Gly Asp Leu Asp Ile Ser Asp Thr Val Gly Val 20 25 30

Ser Phe Trp Leu Val Thr Ala Gly Met Leu Ala Ala Thr Val Phe Phe 35 40 45

Phe Val Glu Arg Asp Gln Val Ser Ala Glu Trp Lys Thr Ser Leu Thr 50 55 60

Val Ser Gly Leu Ile Thr Gly Ile Ala Phe Trp His Tyr Leu Tyr Met 65 70 75 80

Arg Gly Val Trp Ile Asp Thr Gly Asp Thr Pro Thr Val Phe Arg Tyr 85 90 95

Ile Asp Trp Leu Leu Thr Val Pro Leu Gln Met Val Glu Phe Tyr Leu 100 105 110

Ile Leu Ala Ala Cys Thr Ser Val Ala Ala Ser Leu Phe Lys Lys Leu 115 120 125

Leu Ala Gly Ser Leu Val Met Leu Gly Ala Gly Phe Ala Gly Glu Ala
130 135 140

Gly Leu Ala Pro Val Leu Pro Ala Phe Ile Ile Gly Met Ala Gly Trp-145 150 155 160

Leu Tyr Met Ile Tyr Glu Leu Tyr Met Gly Glu Gly Lys Ala Ala Val

165 170 175

Ser Thr Ala Ser Pro Ala Val Asn Ser Ala Tyr Asn Ala Met Met Met 180 185 190

Ile Ile Val Val Gly Trp Ala Ile Tyr Pro Ala Gly Tyr Ala Ala Gly
195 200 205

Tyr Leu Met Gly Gly Glu Gly Val Tyr Ala Ser Asn Leu Asn Leu Ile 210 215 220

Tyr Asn Leu Ala Asp Phe Val Asn Lys Ile Leu Phe Gly Leu Ile Ile 225 230 235. 240

Trp Asn Val Ala Val Lys Glu Ser Ser Asn Ala 245 250

. . . . . .

<210> 52

<211> 753

<212> DNA

<213> Naturally occurring gamma proteobacterium

<220>

<221> CDS

<222> (1)..(753)

<223> Proteorhodopsin variant from pcr clone PALB5; GenBank#AF349997

<400> 52

atg ggt aaa tta tta ctg ata tta ggt agt gct att gca ctt cca tca 48
Met Gly Lys Leu Leu Ile Leu Gly Ser Ala Ile Ala Leu Pro Ser
1 10 15

ttt gct gct gct ggt ggc gat cta gat ata agt gat act gtt ggt gtt

Phe Ala Ala Gly Gly Asp Leu Asp Ile Ser Asp Thr Val Gly Val

20 25 30

tca ttc tgg ctg gtt aca gct ggt atg tta gcg gca act gtg ttc ttt

Ser Phe Trp Leu Val Thr Ala Gly Met Leu Ala Ala Thr Val Phe Phe

35 40 45

ttt gta gaa aga gac caa gtc agc gct aag tgg aaa act tca ctt act

192
Phe Val Glu Arg Asp Gln Val Ser Ala Lys Trp Lys Thr Ser Leu Thr

50

55

60

gta tct ggt tta att act ggt ata gcc ttt tgg cat tat ctc tat atg 240

Val 65	Ser	Gly	Leu	Ile	Thr 70	Gly	Ile	Ala	Phe	Trp 75	His	Tyr	Leu	Tyr	Met 80		
				ata Ile 85													288
				tta Leu													336
				tgt Cys													384
				tta Leu											gct Ala		432
				gta Val											tgg Trp 160		480
				tat Tyr 165	Glu												528
				cct Pro													576
				gga Gly													624
				Gly													672
				gac Asp													720
				gtt Val 245								fruit n				•,	753

<210> 53

<211> 251 <212> PRT

<213> Naturally occurring gamma proteobacterium

<400> 53

Met Gly Lys Leu Leu Leu Ile Leu Gly Ser Ala Ile Ala Leu Pro Ser 1 5 10 15

Phe Ala Ala Gly Gly Asp Leu Asp Ile Ser Asp Thr Val Gly Val 20 25 30

Ser Phe Trp Leu Val Thr Ala Gly Met Leu Ala Ala Thr Val Phe Phe 35 40 45

Phe Val Glu Arg Asp Gln Val Ser Ala Lys Trp Lys Thr Ser Leu Thr 50 55 60

Val Ser Gly Leu Ile Thr Gly Ile Ala Phe Trp His Tyr Leu Tyr Met 65 70 75 80

Arg Gly Val Trp Ile Asp Thr Gly Asp Thr Pro Thr Val Phe Arg Tyr 85 90 95

Ile Asp Trp Leu Leu Thr Val Pro Leu Gln Met Val Glu Phe Tyr Leu 100 105 110

Ile Leu Ala Ala Cys Thr Asn Val Ala Ala Ser Leu Phe Lys Lys Leu 115 120 125

Leu Ala Gly Ser Leu Val Met Leu Gly Ala Gly Phe Ala Gly Glu Ala 130 135 140

Gly Leu Ala Pro Val Trp Pro Ala Phe Ile Ile Gly Met Ala Gly Trp 145 150 155 160

Leu Tyr Met Ile Tyr Glu Leu Tyr Met Gly Glu Gly Lys Ala Ala Val 165 170 175

Ser Thr Ala Ser Pro Ala Val Asn Ser Ala Tyr Asn Ala Met Met Met-180 185 190

Ile Ile Val Val Gly Trp Ala Ile Tyr Pro Ala Gly Tyr Ala Ala Gly

195 200 205

Tyr Leu Met Gly Gly Glu Gly Val Tyr Ala Ser Asn Leu Asn Leu Ile 210 215 220

Tyr Asn Leu Ala Asp Phe Val Asn Lys Ile Leu Phe Gly Leu Ile Ile 225 230 235 240

Trp Asn Val Ala Val Lys Glu Ser Ser Asn Ala 245 250

<210> 54

<211> 753

<212> DNA

<213> Naturally occurring gamma proteobacterium

<220>

<221> CDS

<222> (1)..(753)

<223> Proteorhodopsin variant from pcr clone PalB7; GenBank #AF349999

<400> 54

atg ggt aaa tta tta ctg ata tta ggt agt gct att gcg ctt cca tca 48
Met Gly Lys Leu Leu Leu Gly Ser Ala Ile Ala Leu Pro Ser
1 5 10 15

ttt gct gct gct ggc gat cta gat ata agt gat act gtt ggt gtt

Phe Ala Ala Gly Gly Asp Leu Asp Ile Ser Asp Thr Val Gly Val

20 25 30

tca ttc tgg ctg gtt acg gct ggt atg tta gcg gca act gta ttc ttt

Ser Phe Trp Leu Val Thr Ala Gly Met Leu Ala Ala Thr Val Phe Phe

35

40

45

ttt gta gaa aga gac caa gtc agc gct aag tgg aaa act tca ctt act

Phe Val Glu Arg Asp Gln Val Ser Ala Lys Trp Lys Thr Ser Leu Thr

50 55 60

gta tct ggt tta att act ggt ata gct ttt tgg cat tat ctc tac atg
Val Ser Gly Leu Ile Thr Gly Ile Ala Phe Trp His Tyr Leu Tyr Met
65 70 75 80

aga ggt gtt tgg ata gat act ggt gat aca cca aca gta ttt aga tat

288
Arg Gly Val Trp Ile Asp Thr Gly Asp Thr Pro Thr Val Phe Arg Tyr

85
90
95

att gat tgg tta tta act gtt cca tta caa atg gtt gag ttc tat cta 336

Ile	Asp	Trp	Leu 100	Leu	Thr	Val	Pro	Leu 105	Gln	Met	Val	Glu	Phe 110	Tyr	Leu		
				tgt Cys													384
				ttg Leu													432
				gta Val													480
				tat Tyr 165													528
				cct Pro												3 .	576
				gga Gly													624
				ggc Gly													672
				gac Asp													720
				gtt Val 245									•				753
<21	-	55														•	

<211> 251

<212> PRT

<213> Naturally occurring gamma proteobacterium

<400> 55

Met Gly Lys Leu Leu Leu Ile Leu Gly Ser Ala Ile Ala Leu Pro Ser 1 10 15

Phe Ala Ala Gly Gly Asp Leu Asp Ile Ser Asp Thr Val Gly Val

20

25

30

Ser Phe Trp Leu Val Thr Ala Gly Met Leu Ala Ala Thr Val Phe Phe 35 40 45

Phe Val Glu Arg Asp Gln Val Ser Ala Lys Trp Lys Thr Ser Leu Thr 50 55 60

Val Ser Gly Leu Ile Thr Gly Ile Ala Phe Trp His Tyr Leu Tyr Met 65 70 75 80

Arg Gly Val Trp Ile Asp Thr Gly Asp Thr Pro Thr Val Phe Arg Tyr 85 90 95

Ile Asp Trp Leu Leu Thr Val Pro Leu Gln Met Val Glu Phe Tyr Leu 100 105 110

Ile Leu Ala Ala Cys Thr Ser Val Ala Ala Ser Leu Phe Lys Lys Leu 115 120 125

Leu Ala Gly Ser Leu Val Met Leu Gly Ala Gly Ser Ala Gly Glu Ala: 130 135 140

Gly Leu Ala Pro Val Leu Pro Ala Phe Ile Ile Gly Met Ala Gly Trp 145 150 155 160

Leu Tyr Met Ile Tyr Glu Leù Tyr Met Gly Glu Gly Lys Ala Ala Val 165 170 175

Ser Thr Ala Ser Pro Ala Val Asn Ser Ala Tyr Asn Ala Met Met Met 180 185 190

Ile Ile Val Val Gly Trp Ala Ile Tyr Pro Ala Gly Tyr Ala Ala Gly
195 200 205

Tyr Leu Met Gly Gly Glu Gly Val Tyr Ala Ser Asn Leu Asn Leu Ile 210 215 220

Tyr Asn Leu Ala Asp Phe Val Asn Lys Ile Leu Phe Gly Leu Ile Ile

225 230 235 240

Trp Asn Val Ala Val Lys Glu Ser Ser Asn Ala 245 250

<210 <211 <212 <213	.> ' !> !	56 753 DNA Natur	rally	7 000	urri	ing g	jamma	ı pro	teok	pacte	erium	n				· .
<220 <221 <222 <223	-> ( ?>	CDS (1) Prote			sin v	varia	ent f	from	pcr	clor	ne Pa	a1B6;	Ger	ıBanl	: # A	F349998
<400	) <b>&gt;</b>	56														
atg	ggt	aaa Lys														48
ttt Phe	gct Ala	gct Ala	gct Ala 20	ggt Gly	ggc Gly	gat Asp	cta Leu	gat Asp 25	ata Ile	agt Ser	gat Asp	act Thr	gtt Val 30	ggt Gly	gtt Val	96
		tgg Trp 35														144
		gaa Glu														192
		ggt Gly														240
		gtt Val														288
		tgg Trp														336
		gct Ala														384

125

120

115

•											
					tta Leu						432
					gct Ala						480
					tat Tyr						528
					aac Asn						576
					att Ile 200						624
					gta Val						672
					aac Asn						720
	-	_	_	_	tct Ser				,		753

<210> 57

<211> 251

<212> PRT

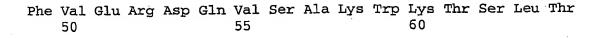
<213> Naturally occurring gamma proteobacterium

<400> 57

Met Gly Lys Leu Leu Leu Ile Leu Gly Ser Ala Ile Ala Leu Pro Ser 1 5 10 15

Phe Ala Ala Gly Gly Asp Leu Asp Ile Ser Asp Thr Val Gly Val 20 25 30

Ser Phe Trp Leu Val Thr Ala Gly Met Leu Ala Ala Thr Val Phe Phe 35 40 45



Val Ser Gly Leu Ile Thr Gly Ile Ala Phe Trp His Tyr Leu Tyr Met 65 70 75 80

Arg Gly Val Trp Ile Asp Thr Gly Asp Thr Pro Thr Val Phe Arg Tyr 85 90 95

Ile Asp Trp Leu Leu Thr Val Pro Leu Gln Met Val Glu Phe Tyr Leu 100 105 110

Ile Leu Ala Ala Cys Thr Asn Val Ala Ala Ser Leu Phe Lys Lys Leu 115 120 125

Leu Ala Gly Ser Leu Val Met Leu Gly Ala Gly Phe Ala Gly Glu Ala 130 135 140

Gly Leu Ala Pro Val Trp Pro Ala Phe Ile Ile Gly Met Ala Gly Trp 145 150 155 160

Leu Tyr Met Ile Tyr Glu Leu Tyr Met Gly Glu Gly Lys Ala Ala Val 165 170 175

Ser Thr Ala Ser Pro Ala Val Asn Ser Ala Tyr Asn Ala Met Met Val 180 185 190

Ile Ile Val Val Gly Trp Ala Ile Tyr Pro Ala Gly Tyr Ala Ala Gly
195 200 205

Tyr Leu Met Gly Gly Glu Gly Val Tyr Ala Ser Asn Leu Asn Leu Ile 210 215 220

Tyr Asn Leu Ala Asp Phe Val Asn Lys Ile Leu Phe Gly Leu Ile Ile 225 230 235 240

Trp Asn Val Ala Val Lys Glu Ser Ser Asn Ala 245 250

<210> <211> <212> <213>	58 753 DNA Natu	rally	, , oc	curri	ing (	yamma	a pro	oteol	oacto	eria						
<220> <221> <222> <223>	CDS (1). Prot			sin v	varia	ant :	from	pcr	clo	ne Pa	alB8	; Gei	nBanl	k #AE	r3500	00
<400> atg gg Met Gl	t aaa															48
ttt gc Phe Al		_			_		_		_	_		_				96
tca tt Ser Ph																144
ttt gt Phe Va 50	1 <b>G</b> lu	_	_		-	_	-									192.
gta tc Val Se 65															-	240
aga gg Arg Gl	_						_									288
att ga Ile As					_				_							336
att ct Ile Le																384
cta gc Leu Al 13	a Gly															432
gga tt Gly Le 145																480

50

tta tac atg att tat gag cta tat atg ggt gaa ggt aag gct gct gta Leu Tyr Met Ile Tyr Glu Leu Tyr Met Gly Glu Gly Lys Ala Ala Val 165 170 175	528
agt act gca agt cct gct gtt aac tct gca tac aac gca atg atg ser Thr Ala Ser Pro Ala Val Asn Ser Ala Tyr Asn Ala Met Met Met 180 185 190	576
att att gtt gtt gga tgg gca att tat cct gct gga tat gct gct ggt Ile Ile Val Val Gly Trp Ala Ile Tyr Pro Ala Gly Tyr Ala Ala Gly 195 200 205	624
tac cta atg ggt ggc gaa ggt gta tac gct tca aac tta aac ctt ata Tyr Leu Met Gly Gly Glu Gly Val Tyr Ala Ser Asn Leu Asn Leu Ile 210 215 220	672
tat aac ctt gct gac ctt gtt aac aag att cta ttt ggt ttg atc att Tyr Asn Leu Ala Asp Leu Val Asn Lys Ile Leu Phe Gly Leu Ile Ile 225 230 235 240	720
tgg aat gtt gct gtt aaa gaa tct tct aat gct Trp Asn Val Ala Val Lys Glu Ser Ser Asn Ala 245 250	753
<210> 59 <211> 251 <212> PRT <213> Naturally occurring gamma proteobacteria	
<400> 59	
Met Gly Lys Leu Leu Ile Leu Gly Ser Ala Ile Ala Leu Pro Ser 1 5 10 15	
Phe Ala Ala Gly Gly Asp Leu Asp Ile Ser Asp Thr Val Gly Val 20 25 30	
Ser Phe Trp Leu Val Thr Ala Gly Met Leu Ala Ala Thr Val Phe Phe 35 40 45	

60

Phe Val Glu Arg Asp Gln Val Ser Ala Lys Trp Lys Thr Ser Leu Thr

Val Ser Gly Leu Ile Thr Gly Ile Ala Phe Trp His Tyr Leu Tyr Met 65 70 75 80

55

Arg Gly Val Trp Ile Asp Thr Gly Asp Thr Pro Thr Val Phe Arg Tyr 90 85 Ile Asp Trp Leu Leu Thr Val Pro Leu Gln Met Val Glu Phe Tyr Leu 100 105 Ile Leu Ala Ala Cys Thr Ser Val Ala Ala Ser Leu Phe Lys Lys Leu Leu Ala Gly Ser Leu Val Met Leu Gly Ala Gly Phe Ala Gly Glu Ala 135 140 Gly Leu Ala Pro Val Leu Pro Ala Phe Ile Ile Gly Met Ala Gly Trp 145 150 155 160 Leu Tyr Met Ile Tyr Glu Leu Tyr Met Gly Glu Gly Lys Ala Ala Val 165 170 Ser Thr Ala Ser Pro Ala Val Asn Ser Ala Tyr Asn Ala Met Met Met 180 185 190 Ile Ile Val Val Gly Trp Ala Ile Tyr Pro Ala Gly Tyr Ala Ala Gly 200 195 205 Tyr Leu Met Gly Gly Glu Gly Val Tyr Ala Ser Asn Leu Asn Leu Ile 210 215 Tyr Asn Leu Ala Asp Leu Val Asn Lys Ile Leu Phe Gly Leu Ile Ile 225 230 235 Trp Asn Val Ala Val Lys Glu Ser Ser Asn Ala 245

<210> 60 <211> 753

<212> DNA

<213> Naturally occurring gamma proteobacteria

<220>

<221> CDS

<222> (1)..(753)

PCT/US01/14394

<223> Proteorhodopsin variant from pcr clone PalE1;GenBank# AF350001

atg		aaa									ctt Leu			<b>48</b>
	-	_				_		_		 _	gtt Val 30		_	96
				_				_			gtg Val			144
	_	-	_	_		-	-	_	_		tca Ser			192
											ctc Leu			240
											ttc Phe	Arg		288
											ttc Phe 110		cta Leu	336
											aag Lys			384
					-	_					 ggc Gly			432
							-				gct Ala			480
								_		_	gct Ala			528
											atg Met 190			57.6

			cct gct gga Pro Ala Gly		
			gct tca aac Ala Ser Asn 220		
		Val Asn Lys	att cta ttt Ile Leu Phe 235		
		gaa tct tct Glu Ser Ser	-		753
<210> 61 <211> 251 <212> PRT <213> Natu	rally occurr	ing gamma pr	oteobacteria	`	
<400> 61	,				
Met Gly Lys 1	Leu Leu Leu 5	Ile Leu Gly	Ser Ala Ile 10	Ala Leu Pr 15	
Phe Ala Ala	Ala Gly Gly 20	Asp Leu Asp 25	Ile Ser Asp	Thr Val Gl	y Val
Ser Phe Trp 35	Leu Val Thr	Ala Gly Met	Leu Ala Ala	Thr Val Ph	e Phe
Phe Val Glu 50	Arg Asp Gln	Val Ser Ala 55	Lys Trp Lys	Thr Ser Le	u Thr
Val Ser Gly 65	Leu Ile Thr	Gly Ile Ala	Phe Trp His 75	Tyr Leu Ty	r Met 80
Arg Gly Val	Trp Ile Asp	Thr Gly Asp	Thr Pro Thr 90	Val Phe Ar 95	
Ile Asp Trp	Leu Leu Thr	Val Pro Leu 105	Gln Val Val	Glu Phe Ty 110	r Leu

Ile Leu Ala Ala Cys Thr Ser Val Ala Ala Ser Leu Phe Lys Lys Leu 115 120 125 Leu Ala Gly Ser Leu Val Met Leu Gly Ala Gly Phe Ala Gly Glu Ala 130 135 Gly Leu Ala Pro Val Leu Pro Ala Phe Ile Ile Gly Met Ala Gly Trp 145 Leu Tyr Met Ile Tyr Glu Leu Tyr Met Gly Glu Gly Lys Ala Ala Val 165 170 Ser Thr Ala Ser Pro Ala Val Asn Pro Ala Tyr Asn Ala Met Met Met 180 185 Ile Ile Val Val Gly Trp Ala Ile Tyr Pro Ala Gly Tyr Ala Ala Gly 195 200 205 Tyr Leu Met Gly Gly Glu Gly Val Tyr Ala Ser Asn Leu Asn Leu Ile 210 215 220 Tyr Asn Leu Ala Asp Phe Val Asn Lys Ile Leu Phe Gly Leu Ile Ile 225 230 235 Trp Asn Val Ala Val Lys Glu Ser Ser Asn Ala 245 <210> 62 <211> 753 <212> DNA <213> Naturally occurring gamma proteobacterium <220> <221> CDS <222> (1)..(753) <223> Proteorhodopsin variant from pcr clone PalE6; GenBank#AF350002 <400> 62 atg ggt aaa tta tta ctg ata tta ggt agt gct att gca ctt cca tca 48 Met Gly Lys Leu Leu Ile Leu Gly Ser Ala Ile Ala Leu Pro Ser 10

the got got got ggt ggc gat cha gat and agt gat act git ggt git he Ala Ala Gly Gly Asp Leu Asp Tle Ser Asp Thr Val Gly Val 20  to the tog ctg git aca gct ggt atg the gcg gca act git the tit tit Ser Phe Trp Leu Val Thr Ala Gly Met Leu Ala Ala Thr Val Phe Phe Ala Ala Glu Arg Asp Gln Val Ser Ala Lys Trp Lys Thr Ser Leu Thr 50  gta tot ggt the att act ggt ata gct tit tit tit gg cat the tot tact the Ser Gly Leu Ile Thr Gly Ile Ala Phe Trp His Tyr Leu Tyr Met 65  aga ggt gtt tit gg ata gat act ggt gat aca ca aca gta the act disc at Arg Gly Val Trp Ile Asp Thr Gly Asp Thr Pro Thr Val Phe Arg Tyr 90  aga ggt gtt tit att act git coa the ca at git gat the tac the Arg Gly Val Trp Ile Asp Thr Gly Asp Thr Pro Thr Val Phe Arg Tyr 90  att gat tit git the act git coa the cas at git gat the tac the Ile Asp Trp Leu Thr Val Pro Leu Gln Met Val Glu Phe Tyr Leu 100  att ctt got got tit aca agt git got got to the tit the aga agt tit leu Ala Ala Cys Thr Ser Val Ala Ala Ser Leu Phe Lys Lys Leu 115  cta gct ggt to tit did act git git ggt got ggt tit gat ggt git git git git git git git git gi
Ser Phe Trp Leu Val Thr Ala Gly Met Leu Ala Ala Thr Val Phe Phe 45  ttt gta gaa aga gac caa gtc agc gct aag tgg aaa act tca ctt act Phe Val Glu Arg Asp Gln Val Ser Ala Lys Trp Lys Thr Ser Leu Thr 50  gta tct ggt tta att act ggt ata gct ttt tgg cat tat ctc tac atg Val Ser Gly Leu Ile Thr Gly Ile Ala Phe Trp His Tyr Leu Tyr Met 65  aga ggt gtt tgg ata gat act ggt gat aca cca aca gta ttt aga tat Arg Gly Val Trp Ile Asp Thr Gly Asp Thr Fro Thr Val Phe Arg Tyr 90  att gat tgg tta tta act gtt cca tta caa atg gtt gag ttc tat cta Ile Asp Trp Leu Leu Thr Val Pro Leu Gln Met Val Glu Phe Tyr Leu 1100  att ctt gct tgt aca agt gtt gct gct tca tta tta aga agc ctt Ile Leu Ala Ala Cys Thr Ser Val Ala Ala Ser Leu Phe Lys Lys Leu 115  cta gct ggt tca tta/gta atg tta ggt gct gga ttt gca ggc gaa gct Leu Ala Gly Ser Leu Val Met Leu Gly Ala Gly Phe Ala Gly Glu Ala 130  ggt tta gct cct gta tca cct gct tc att att ggt atg ggt ggg ggt tta ggt tta gct ggt tta gct ggt tta gct ggt tta gct ggt tta atg gt ggt gg ggt tta ggt ggt
Fhe Val Glu Arg Asp Gln Val Ser Ala Lys Trp Lys Thr Ser Leu Thr 50    gta tct ggt tta att act ggt ata gct ttt tgg cat tat ctc tac atg   Val Ser Gly Leu Ile Thr Gly Ile Ala Phe Trp His Tyr Leu Tyr Met   65    aga ggt gtt tgg ata gat act ggt gat aca cca aca gta ttt aga tat   Arg Gly Val Trp Ile Asp Thr Gly Asp Thr Pro Thr Val Phe Arg Tyr   85    att gat tgg tta tta act gtt cca tta caa atg gtt gag ttc tat cta   Ile Asp Trp Leu Leu Thr Val Pro Leu Gln Met Val Glu Phe Tyr Leu   100    att ctt gct gct tgt aca agt gtt gct gct tca tta tag aag ctt   Ile Leu Ala Ala Cys Thr Ser Val Ala Ala Ser Leu Phe Lys Leu   115    cta gct ggt tca tta cct gct gt atg ggt gct gga ttt gca ggc gaa gct   Leu Ala Gly Ser Leu Val Met Leu Gly Ala Gly Phe Ala Gly Glu Ala   130    ggt tta gct cct gta tta cct gct ttc att att gg gg gga gg
Val Ser Gly Leu Ile Thr Gly Ile Ala Phe Trp His Tyr Leu Tyr Met 80  aga ggt gtt tgg ata gat act ggt gat aca cca aca gta ttt aga tat Arg Gly Val Trp Ile Asp Thr Gly Asp Thr Pro Thr Val Phe Arg Tyr 95  att gat tgg tta tta act gtt cca tta caa atg gtt gag tta tat cta Ile Asp Trp Leu Leu Thr Val Pro Leu Gln Met Val Glu Phe Tyr Leu 100  att ctt gct gct tgt aca agt gtt gct gct tca tta ttt aag aag ctt Ile Leu Ala Ala Cys Thr Ser Val Ala Ala Ser Leu Phe Lys Lys Leu 115  cta gct ggt tca tta/gta atg tta ggt gct gga ttt gca ggc gaa gct Ala Gly Ser Leu Val Met Leu Gly Ala Gly Phe Ala Gly Glu Ala 130  ggt tta gct cct gta tta cct gct ttc att att att ggt atg gct gga ttg Gly Leu Ala Pro Val Leu Pro Ala Phe Ile Ile Gly Met Ala Gly Trp 145  tta tac atg att tat gag cta cat atg ggt gaa ggt aag gct gga tgg Gly Leu Tyr Met Ile Tyr Glu Leu His Met Gly Glu Gly Lys Ala Ala Val 165  agt act gca agt cct gct gta act ct gca tac aac gca atg atg aag Ser Thr Ala Ser Pro Ala Val Asn Ser Ala Tyr Asn Ala Met Met Lys 185  att att gtt att gga tgg gca att tac ct gct gga tat gct gga tat gct gcd gtl Ile Ile Val Ile Gly Trp Ala Ile Tyr Pro Ala Gly Tyr Ala Ser Asn Leu Asn Leu Ile Ile Tyr Leu Met Ser Gly Asp Gly Val Tyr Ala Ser Asn Leu Asn Leu Ile  Tyr Leu Met Ser Gly Asp Gly Val Tyr Ala Ser Asn Leu Asn Leu Ile  Tyr Leu Met Ser Gly Asp Gly Val Tyr Ala Ser Asn Leu Asn Leu Ile  Tyr Leu Met Ser Gly Asp Gly Val Tyr Ala Ser Asn Leu Asn Leu Ile
Arg Gly Val Trp Ile Asp Thr Gly Asp Thr Pro Thr Val Phe Arg Tyr 95  att gat tgg tta tta act gtt cca tta caa atg gtt gag ttc tat cta 100 100 100 100 100 100 100 100 100 10
The Asp Trp Leu Leu Thr Val Pro Leu Gln Met Val Glu Phe Tyr Leu 100 att ctt gct gct tgt aca agt gtt gct gct tca tta ttt aag aag ctt Ile Leu Ala Ala Cys Thr Ser Val Ala Ala Ser Leu Phe Lys Lys Leu 120 at a gct ggt tca tta/gta atg tta ggt gct gga ttt gca ggc gaa gct Leu Ala Gly Ser Leu Val Met Leu Gly Ala Gly Phe Ala Gly Glu Ala 130 at 135 at at ggt gct gg at ggt ggt gg atg gct gg atg ggt tta gct cct gta tta cct gct ttc att att ggt atg gct gga ttg ggt gg atg gct ggy Leu Ala Pro Val Leu Pro Ala Phe Ile Ile Gly Met Ala Gly Trp 150 at at at at at at at ac atg att tat gag cta cat atg ggt gaa ggt ag gct gg atg seg gat ag gct gct gra leu Tyr Met Ile Tyr Glu Leu His Met Gly Glu Gly Lys Ala Ala Val 165 at at att gtt att gga tgg gca att tat cct gca tac aac gca atg atg and Ser Thr Ala Ser Pro Ala Val Asn Ser Ala Tyr Asn Ala Met Met Lys 180 att att gtt att gga tgg gca att tat cct gct gga tag gct gct ggt Ile Ile Val Ile Gly Trp Ala Ile Tyr Pro Ala Gly Tyr Ala Ala Gly 195 at ac cta atg ggt gac ggt ta ac ctc aac tta aac ctt ata Gra atg atg ggt gac ggt gta tac cta aac tta aac ctt ata Gra atg atg ggt gac ggt gta tac cta aac tta aac ctt ata Gra atg Tyr Leu Met Ser Gly Asp Gly Val Tyr Ala Ser Asn Leu Asn Leu Ile
The Leu Ala Ala Cys Thr Ser Val Ala Ala Ser Leu Phe Lys Lys Leu 115
Leu Ala Gly Ser Leu Val Met Leu Gly Ala Gly Phe Ala Gly Glu Ala 130 135 140 140 135 140 140 135 140 140 135 140 140 140 140 150 155 140 140 140 140 140 140 140 140 140 140
Gly Leu Ala Pro Val Leu Pro Ala Phe Ile Ile Gly Met Ala Gly Trp 145
Leu Tyr Met Ile Tyr Glu Leu His Met Gly Glu Gly Lys Ala Ala Val 165
Ser Thr Ala Ser Pro Ala Val Asn Ser Ala Tyr Asn Ala Met Met Lys 180  att att gtt att gga tgg gca att tat cct gct gga tat gct gct ggt Ile Ile Val Ile Gly Trp Ala Ile Tyr Pro Ala Gly Tyr Ala Ala Gly 195  tac cta atg agt ggt gac ggt gta tac gct tca aac tta aac ctt ata Tyr Leu Met Ser Gly Asp Gly Val Tyr Ala Ser Asn Leu Asn Leu Ile
Ile Ile Val Ile Gly Trp Ala Ile Tyr Pro Ala Gly Tyr Ala Ala Gly 195 200 205  tac cta atg agt ggt gac ggt gta tac gct tca aac tta aac ctt ata Tyr Leu Met Ser Gly Asp Gly Val Tyr Ala Ser Asn Leu Asn Leu Ile
Tyr Leu Met Ser Gly Asp Gly Val Tyr Ala Ser Asn Leu Asn Leu Ile

		ctt Leu															720
		gtt Val					•			_							753
<210 <211 <212 <213	L> 2 2> 1	63 251 PRT Natur	ally	/ occ	curri	ing g	gamma	a pro	oteok	oacte	∍riur	n					
<400		53						_									
Met 1	Gly	Lys	Leu	Leu 5	Leu	Ile	Leu	Gly	Ser 10	Ala	Ile	Ala	Leu	Pro 15	Ser		
Phe	Ala	Ala	Äla 20	Gly	Gly	Asp	Leu	Asp 25	Ile	Ser	Asp	Thr	Val 30	Gly	Val		÷ .
Ser	Phe	Trp 35	Leu	Val	Thr	Ala	Gly 40	Met	Leu	Ala	Ala	Thr 45	Val	Phe	Phe		
Phe	Val 50	Glu	Arg	Asp	Gln	Val 55	Ser	Ala	Lys	Trp	Lys 60	Thr	Ser	Leu	Thr		
Val 65	Ser	Gly	Leu	Ile	Thr 70	Gly	Ile	Ala	Phe	Trp 75	His	Tyr	Leu	Tyr	Met 80	•	_
Arg	Gly	Val	Trp	Ile 85	Asp	Thr	Gly	Asp	Thr 90	Pro	Thr	Val	Phe	Arg 95	Tyr		
Ile	qeA	Trp	Leu 100	Leu	Thr	Val	Pro	Leu 105	Gln	Met	Val	Glu	Phe 110	Tyr	Leu		•
Ile	Leu	Ala. 115	Ala	Cys	Thr	Ser	Val 120	Ala	Ala	Ser	Leu	Phe 125	ГЛЗ	Lys	Leu		
Leu	Ala 130	Gly	Ser	Leu	Val	Met 135	Leu	Gly	Ala	Gly	Phe 140	Ala	Gly	Glu	Ala		

Gly Leu Ala Pro Val Leu Pro Ala Phe Ile Ile Gly Met Ala Gly Trp 150 145 155 160 Leu Tyr Met Ile Tyr Glu Leu His Met Gly Glu Gly Lys Ala Ala Val 170 165 Ser Thr Ala Ser Pro Ala Val Asn Ser Ala Tyr Asn Ala Met Met Lys 180 185 Ile Ile Val Ile Gly Trp Ala Ile Tyr Pro Ala Gly Tyr Ala Ala Gly 200 Tyr Leu Met Ser Gly Asp Gly Val Tyr Ala Ser Asn Leu Asn Leu Ile 220 210 215 Tyr Asn Leu Ala Asp Phe Val Asn Lys Ile Leu Phe Gly Leu Ile Ile 230 235 240 225 Trp Asn Val Ala Val Lys Glu Ser Ser Asn Ala <210> 64 <211> 753 <212> DNA <213> Naturally occurring gamma proteobacterium <220> <221> CDS <222> (1)..(753) <223> Proteorhodopsin variant from pcr clone PalE7; GenBank# AF350003 <400> 64 atg ggt aaa tta tta ctg ata tta ggt agt gct att gca ctt cca tca 48 Met Gly Lys Leu Leu Leu Ile Leu Gly Ser Ala Ile Ala Leu Pro Ser 1 ttt get get get gge gat eta gat ata agt gat act gtt ggt gtt 96 Phe Ala Ala Gly Gly Asp Leu Asp Ile Ser Asp Thr Val Gly Val ′ 20 30 25 144 tca ttc tgg ctg gtt aca gct ggt atg tta gcg gca act gtg ttc ttt Ser Phe Trp Leu Val Thr Ala Gly Met Leu Ala Ala Thr Val Phe Phe 35 40 45

	gta Val 50															192
	tct Ser							_							_	240
	ggt Gly															288
	gat Asp					_				_	_					336
	ctt Leu	_	_	-		-	_	_	_				_	_		384
	gct Ala 130				_	_			_			_		_	_	432
	tta Leu	-		_			_					_	-			480
	tac Tyr	-						Met		-						528
-	act Thr		_		_	_			_			_	_	_	_	576
	att Ile															624
	cta Leu 210															672
	aac Asn															720
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170

175

165

Ser	Thr	Ala	Ser	Pro	Ala	Val	Asn	Ser	Ala	Tyr	Asn	Ala	Met	Met	Met
			180					185		•			190		

Ile Ile Val Val Gly Trp Ala Ile Tyr Pro Ala Gly Tyr Ala Ala Gly 195 200 205

Tyr Leu Met Gly Gly Glu Gly Val Tyr Ala Ser Asn Leu Asn Leu Ile 210 215 220

Tyr Asn Leu Ala Asp Phe Val Asn Lys Ile Leu Phe Gly Leu Ile Ile 225 230 235 240

Trp Asn Val Ala Val Lys Glu Ser Ser Asn Ala 245 250